Fulminant liver failure during interferon beta treatment of multiple sclerosis

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Although interferon (IFN) β has many adverse effects, including fulminant liver failure. Interferon therapy is usually limited to autoantibodies with the thyroid the most common target organ involved. Liver abnormalities during IFN β therapy are usually clinically asymptomatic and transient biochemical events. We report a patient who developed acute fulminant liver failure a few weeks after the initiation of IFN β and required an emergency liver transplant. Fulminant failure as a result of IFN β is not well reported in the MS literature and this is the first patient reported who required a liver transplant as a result of MS therapy.

Case report. A 59-year-old Caucasian woman was transferred to the Intensive Care Unit (ICU) in hepatic coma and hepatorenal syndrome 7 weeks after starting interferon β-1a (Rebif, Serono-Canada, Oakville, Ontario, Canada). One year previously, she developed diplopia and ataxia. An MRI scan disclosed small deep white matter lesions consistent with demyelination. Examination of the CSF revealed an immunoglobulin (Ig) G:Albumin index of 0.89 (normal 0.34 to 0.66), an IgG synthesis rate of 10.2 mg/d (normal < 3.4 mg/d), and the presence of oligoclonal bands. Treatment with intermittent corticosteroids was followed by IFN β-1a at a dose of 11 μg subcutaneously three times weekly, escalating to 22 μg subcutaneously three times weekly (total cumulative dose = 215 μg). Her medical history was significant for hypothyroidism. There was no history of liver disease or risk factors for viral infection. The patient did not consume alcohol and acetaminophen use was occasional. Liver biochemistry immediately pre-treatment was normal, specifically serum aspartate transaminase (AST) 18 U/L (normal 0–40 U/L) and alanine transaminase (ALT) 25 U/L (normal < 38 U/L). Three weeks before presentation, she developed anorexia and nausea, and became jaundiced with dark urine and mild pruritus 2 weeks later. She presented to hospital with decreased level of consciousness, responsive only to painful stimuli. The initial serum ALT was 1,360 U/L, AST 1,360 U/L, bilirubin 484 μmol/L (normal < 17 μmol/L), international normalized ratio 8.7 (normal < 1.2), albumin 29 g/L (normal 35 to 45 g/L). Virology for hepatitis B virus (HBV), hepatitis C virus, cytomegalovirus, and Epstein-Barr virus antigen (HHsAg), hepatitis B core antibody (anti-HBc), hepatitis C, and cytomegalovirus was negative as was the serum antinuclear antibody (ANA), anti-smooth muscle antibody, and antismooth-veen screen. The serum antinuclear antibody was positive at a titer of 1:1600. Abdominal ultrasound revealed no features of cirrhosis or portal hypertension. Treatment with lactulose and IV methylprednisolone were started without improvement and the patient required intubation and mechanical ventilated for airway protection. Liver transplantation was performed 3 days after ICU admission. Pathologic examination of the explanted liver revealed submassive hepatic necrosis. The post-transplant course has been uncomplicated except for an episode of acute rejection.

Discussion. Although liver failure is an uncommon but well recognized complication of IFN α during treatment of chronic viral hepatitis, there has been only one report in the literature of liver failure complicating the treatment of MS. In the treatment of chronic viral hepatitis, IFN α has both an antiviral and immunoinhibitory effect, which may result in decomposition in patients with cirrhosis or precipitate liver failure on the basis of autoimmune hepatitis. Despite the similar side effect profile, including autoimmune phenomena, IFN β-induced de novo autoimmune hepatitis has only been reported once.

Our patient is the second to be reported with fulminant liver failure as a direct result of IFN β therapy and is the first to require liver transplantation. It is possible that the mechanism of liver injury in our patient was direct IFN β hepatotoxicity; we suspect, however, that immune-mediated properties of IFN β precipitated acute autoimmune hepatitis. Although the serum ANA and anti-smooth muscle antibodies, classic features of type I autoimmune hepatitis, were negative, these autoantibodies are not present in non–type I autoimmune hepatitis. Moreover, there was a history of hypothyroidism and a positive serum antinuclear, and antihistone antibodies, which has been reported in association with autoimmune hepatitis, suggesting a background milieu of autoimmune predisposition.

Our experience suggests that although liver enzyme elevations during IFN β therapy can be transient, liver failure can occur. We suggest that patients taking IFN β for MS should have their liver enzymes closely monitored. In the situation of significant elevations, IFN β should be withheld and the patients followed for evidence of liver failure.

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References


An ursatrical IgE-mediated reaction to interferon β-1b

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An authoritative review of interferon (IFN) β toxicity in the treatment of MS stated that type I or IV allergic reactions have not been observed or reported.1 Our recent experience provides the opportunity to reexamine this important point. We report a woman with MS who manifested a type I, IgE-mediated, allergic response to the protein IFN β-1b.

Case report. A 32-year-old woman had three discrete episodes of nonstereotyped neurologic deficit over 9 years. Her brain and spinal MRI results were consistent with demyelinating disease. Although she declined lumbar puncture, we considered relapsing-remitting MS to be an appropriate diagnosis given her clinical history and imaging database. After beginning IFN β-1b, the injections evoked multiple side effects: flulike symptoms requiring nonsteroidal anti-inflammatory drugs, urinary urgency with incomplete bladder evacuation lasting 4 hours after each injection, leg cramps, and exacerbation of preexisting asthma. She had previously required albuterol therapy and short courses of antibiotics for asthmatic exacerbations that typically lasted 7 days. After IFN β-1b administration, her asthmatic exacerbations lasted approximately 1 month, were less responsive to albuterol, required longer antibiotic courses, and sometimes required oral steroids. Additionally, she noted more difficulty breathing each day she received her injection. These side effects were all eliminated by decreasing the IFN β-1b dosage by 75%. Thereafter, she gradually resumed the full IFN β-1b dose, usually with fewer problems. Her atopic history was also significant for multiple drug allergies, including both angioedema and urticaria in response to penicillin. After approximately 9 months of IFN β-1b treatment, she de-