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LETTER TO EDITOR

Interferon-β 1b Augments Pulse Steroid-Associated Hepatoxicity

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To the Editor,

Methylprednisolone and interferon-β 1b are the two drugs frequently used in the treatment of multiple sclerosis (MS). However, both drugs rarely cause liver toxicity [1, 2]. Herein, we present a patient with MS who developed severe hepatotoxicity while using interferon after pulse methylprednisolone therapy.

A 28-year-old woman was visited in the Gastroenterology Outpatient Clinic because of elevated liver enzymes after intake of interferon-β 1b for attack of MS on May 2007. In her past medical history, she was diagnosed with MS in August 2006. After the diagnosis, she received 1000 mg per day intravenous methylprednisolone for seven consecutive days. During the steroid therapy, her liver function tests were normal. In October 2006, she had a second attack of MS and received another course of 1000 mg per day methylprednisolone therapy. However, on the third day of the treatment (November 2006), her liver enzymes elevated. She developed her third attack in March 2007 when she received 1000 mg per day methylprednisolone for five consecutive days. She began to use 0.3 mg interferon-β 1b (Betaferon) every other day, at the beginning of April 2007 (two weeks after methylprednisolone therapy). The baseline liver function tests were normal. One month after beginning of interferon-β 1b, serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were increased. The overall follow-up course of the patient is summarized in Table 1.

On admission to the Gastroenterology Ward, she had no complaints and her physical examination was normal. She denied abuse of illicit drugs or alcohol. She had no history of liver disease or drug reaction. She was not taking any concomitant drugs, vitamins or herbal supplements. Complete blood count, prothrombin time and biochemical tests other than liver enzymes were within normal limits. Viral (hepatitis serology and atypical viral serologies including Epstein-Barr virus [EBV], cytomegalovirus [CMV] and herpes simplex virus [HSV]) and autoimmune serologies were all negative. The serum level of immunoglobulin G (IgG), ceruloplasmin and α_1-antitrypsin, iron profile, thyroid function tests were also normal. Hepatobiliary ultrasonography was normal too. Interferon-β 1b was discontinued.

Her liver enzymes continued to rise and peaked on the 17th day after cessation of the therapy. She had an ALT of 875 (Nl: <41) IU/L, AST of 501 (Nl: <40) IU/L, γ-glutamyl transferase (GGT) of 111 (Nl: <55) U/L, total bilirubin of 4.66 (Nl: < 1.1) mg/dL, direct bilirubin of 3 (Nl: <0.3) mg/dL and prothrombin time of 21 (Nl: 10-14) sec. Liver biopsy performed showed moderate lobular inflammation, centrilobular confluent necrosis, bridging necrosis accompanied with porto-portal and porto-central fibrosis. After some supportive management, prothrombin time returned to normal

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Table 1. Liver enzymes during follow-up.

Time	ALT (Nl:<41)	AST (Nl:<40)	GGT (Nl:<55)	ALP (Nl:<270)	Total bilirubin (Nl: 0.1-1)	Direct bilirubin (Nl: < 0.4)
At the time of MS diagnosis (Aug 2006)	8	13	-	-	-	-
3rd day of the 2nd pulse therapy (Nov 2006)	288	111	74	166	0.9	0.4
Two months after steroid therapy (Jan 2007)	14	17	-	-	-	-
3rd pulse therapy (Mar 2007)	10	13	-	-	-	-
1 month after beginning of IFN (May 2007)	338	207	96	-	1.5	0
17th day after stopping IFN (May 2007)	875	501	111	89	4.6	3
1½ month after stopping IFN (Jul 2007)	21	22	56	185	0.8	0.5
3 months after restart of IFN (Nov 2007)	18	17	32	123	0.8	0.5

within five days, and liver enzymes gradually decreased back to normal in July 2007. Because of her neurological status, interferon-β 1b was restarted with the same dose. Her liver enzymes were within normal limits for six months while using the drug.

Our diagnosis in this patient was methylprednisolone-induced hepatitis. Both of methylprednisolone and interferon-β 1b may play a role in developing hepatotoxicity-methylprednisolon triggered and interferon augmented the toxicity.

Steroids are usually safe with regard to hepatotoxicity and they are the treatment of choice if the hepatitis is severe. On the contrary, to the best of our knowledge, there are four cases of methylprednisolone-induced hepatotoxicity [(1)]. The exact mechanism of steroid-related hepatotoxicity is not still known. The idiosyncratic reaction to steroids or its metabolites may be the cause.

Interferon-β 1b is generally well tolerated and the common adverse events are clinically manageable. Elevated liver enzymes occur in 3%-10% of patients [(2)]. Liver abnormalities during inteferon-β therapy are usually asymptomatic with transient biochemical changes. Most of symptomatic liver abnormalities have been reported in patients receiving interferonβ 1a. To the best of our knowledge, only one patient has been reported with interferon-β 1b-induced hepatotoxicity [(3)]. In that patient, thyroid and liver dysfuction occured as a result of autoimmune reaction; hepatic enzymes had three- to four-fold increase.

Although the mechanism of interferon-β-induced hepatotoxicity in MS is mot well-understood, it may be due to idiosyncratic reaction, a hypersensivity reaction or autoimmune reaction [(4)]. The presentation of our patient is more consistent with an idiosyncratic reaction; there was no evidence of autoimmune reaction. Furthermore, genetic defects may result in production of defective enzymes or alteration in the major histocompatibility complex (MHC) class I and II cell receptors which may increase an individual's susceptibility to develop liver injury from multiple drugs which could account for recurrent hepatotoxicity following exposure to interferon-β 1b.

In our patient, the degree of hepatotoxicity after administration of interferon-β 1b following methylprednisolone therapy was more than the degree of hepatotoxicity due to methylprednisolone alone. We believe that interferon-β 1b augmented degrees of hepatotoxicity that caused by methylprednisolone. Therefore clinicans should monitor liver enzymes closely when using interferon-β 1b following pulse methylprednisolone therapy.

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