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CASE REPORT

# Hepatotoxicity case due to interferon beta-1a use

## İnterferon beta-1a kullanımına bağlı gelişen hepatotoksisite vakası

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Interferon β-1a is an immunomodulatory drug widely used in the treatment of multiple sclerosis. Liver dysfunction is a common side effect of this drug and usually develops within the first 6 months of starting interferon therapy. Here, we present our case who developed hepatotoxicity secondary to interferon β-1a treatment.

**Key words:** Multiple sclerosis, liver dysfunction, interferon β

İnterferon β-1a, multipl skleroz tedavisinde yaygın olarak kullanılan immünomodülatör bir ilaçtır. Karaciğer fonksiyon bozukluğu bu ilacın yaygın bir yan etkisi olup genellikle interferon tedavisine başlandıktan sonraki ilk 6 ay içinde gelişir. Burada, interferon β-1a tedavisine sekonder hepatotoksisite gelişen vakamızı sunuyoruz.

**Anahtar kelimeler:** Multipl skleroz, karaciğer fonksiyon bozukluğu, interferon β

## INTRODUCTION

Multiple sclerosis (MS) is an inflammatory and demyelinating disease of the central nervous system that causes neuronal damage and irreversible disability (1). Interferons are a family of cytokines that play a role in the regulation of innate and adaptive immunity. Interferon beta-1a (INFB-1a) is a widely used immunomodulator drug for the treatment of MS (2). It is thought that this drug causes hepatotoxicity by directly damaging hepatocytes or inducing autoimmunity against the liver (3,4). Hepatotoxicity is more common in men, but tends to be more severe in women (5). In patients receiving this therapy, liver dysfunction usually develops within the first 6 months after treatment, and most cases are asymptomatic (3,6-10). In case of excessive elevation of liver enzymes (more than 20 times normal) or jaundice, the drug should be discontinued immediately, in case of mild elevation of enzymes (5 to 20 times the normal value), the dose should be reduced. Enzymes gradually return to normal after dose reduction or discontinuation of the drug (3,6,8,10).

## CASE REPORT

A 21-year-old female patient is being followed up by the neurology department with the diagnosis of multiple sclerosis. Interferon β-1a (Rebif®, Serono) 44 µg three times a week was started 3 months ago. The patient, whose liver function tests were normal before the treatment and in the first two months after the treatment, was sent to our polyclinic in the third month of the treatment due to weakness, nausea, yellowing of the body and dete-

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rioration of liver function tests. The patient, who had no previous liver and biliary tract disease, had no history of alcohol, prescription or over-the-counter drug use. Her physical examination was unremarkable except for jaundice on the sclera and skin. In laboratory tests; alanine aminotransferase (ALT) 528 IU/L, aspartate aminotransferase (AST) 643 IU/L, gamma glutamyl transferase (GGT) 154 IU/L, alkaline phosphatase (ALP) 167 IU/L, serum total bilirubin 15.8 mg/dL and conjugated bilirubin 8.97 mg/dL was found to be pathological. Complete blood count was normal. Viral (hepatitis A, hepatitis B, hepatitis C, cytomegalovirus, Ebstein-Barr virus, rubella virus, herpes virus) and auto-immune markers were negative. There was no pathology in the abdominal ultrasonography. It was thought that hepatotoxicity developed due to the interferon used in the patient. Interferon treatment was discontinued and ursodeoxycholic acid 750 mg/day was started. After the interferon treatment was stopped, the patient's complaints of nausea and fatigue decreased. The patient, whose liver enzymes and bilirubin levels regressed, was discharged on the 6th day of hospitalization and followed up on an outpatient basis. The biochemistry results during the clinical follow-up of the patient are shown in Table 1. Written informed consent was obtained from the patient.

## DISCUSSION

Drug-induced liver injury (DILI) is classified as hepatocellular, cholestatic, and mixed type according to ALT and ALP levels (11). Most cases of DILI are asymptomatic. Those who are symptomatic may present with the usual symptoms of acute liver injury such as fatigue, nausea, abdominal pain, jaundice, itching and dark urine. It may also manifest as acute liver failure, chronic hepatitis and cirrhosis (12). In our case, hepatocellular type liver damage developed due to interferon use. The pathophysiological mechanisms of INFB-1a hepatotoxicity are not fully understood. INFB-1a has a direct toxic effect on hepatocytes. It is thought to cause hepatotoxicity by causing changes in the fine structure of hepatocytes, which play a role in gene expression and protein synthesis, and by suppressing the activity of cytochrome P-450 isoenzymes, which can change the metabolism of other drugs (13-15). Liver dysfunction has been observed frequently in MS patients receiving interferon therapy, and it has been observed that it mostly develops within 6 months of treatment (3,6-10). It is recommended that serum aminotransferase levels be monitored regularly every 3 months during the first year of treatment. If unexplained symptoms of possible liver injury develop, such as fever, mal-

**Table 1** The biochemistry results during the clinical follow-up.

| | During Hospitalization | 1st day | 3rd day | 6th day | 25th day |
|---|---|---|---|---|---|
| AST (U/l) | 643 | 488 | 333 | 251 | 32 |
| ALT (U/l) | 528 | 401 | 295 | 258 | 35 |
| ALP (U/l) | 167 | 137 | 144 | 134 | 117 |
| GGT (U/l) | 154 | 135 | 110 | 94 | 83 |
| Total bilirubin (mg/dl) | 15.8 | 15.5 | 9.78 | 7.09 | 1.54 |
| Direct bilirubin (mg/dl) | 8.97 | 7.58 | 5.33 | 3.71 | 1.22 |

AST: Aspartate aminotransferase (normal value 10-35 U/L), ALT: Alanin aminotransferase (normal value 10-40 U/L), ALP: Alkaline phosphatase (normal value 40-150 U/L), GGT: Gama glutamil transferase (normal value 9-64 U/L

aise, abdominal pain or jaundice, evaluation and follow-up are recommended (16). Elevated liver function tests are usually asymptomatic and enzymes return to normal when treatment is continued or the dose is reduced. Hepatotoxicity, which led to drug discontinuation, developed in less than 1% of patients (6,8). However, more severe symptomatic cases have been reported in the literature, two of which were liver transplant cases.

Elevated liver enzymes due to interferon is a common condition. What makes our case different is the development of hepatotoxicity, which causes discontinuation of the drug, which is less than 1% in the literature. Histopathological examination in the picture of toxic hepatitis does not show which drug caused the damage, but gives important information to the clinician about the type and degree of damage and the course of the disease. Therefore, liver biopsy is not routinely recommended in cases of suspected drug-induced hepatotoxicity. However, in the case of underlying liver disease, liver biopsy may be planned if the clinical picture does not fully explain the drug-induced damage. In our case, the diagnosis of interferon-induced hepatotoxicity was made based on the normal laboratory parameters before interferon treatment, the use of other drugs and alcohol, the absence of liver and biliary tract disease, the absence of other hepatotoxic agents in the investigations for the etiology, and the normalization of liver enzymes and bilirubin values in the follow-ups. In conclusion, hepatotoxicity may develop in MS patients treated with Interferon β-1a. Therefore, MS patients who will receive interferon therapy should be followed up for liver damage before and during treatment.

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