Development of Myasthenia Gravis due to Treatment of Chronic Hepatitis C with a Combination of Interferon-Alpha and Ribavirin

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Dear Sir,

Interferons (IFN) have antiviral and antimitogenic effects and are often used in the treatment of viral hepatitis and some neoplasms. However, they have various side effects including fever, nausea, depression, retinopathy, autoantibodies and autoimmune diseases. Myasthenia gravis (MG) is rarely associated with IFN therapy. Some cases developing MG after IFN or IFN/ribavirin combination therapy for chronic hepatitis C (CHC) have been reported [1–6].

A 48-year-old woman with CHC was treated with 3 million units IFN- α three times a week and 1,000 mg a day ribavirin between 2001 and 2002. No complications were noted during this treatment. At the end of the treatment, a sustained viral response was achieved. One year later, the alanine aminotransferase level was 76 U/l, HCV-RNA had been positive (3×10^6 copies) and liver biopsy had shown hepatic activity index 12 and fibrosis score 2 on the Knodell scale. Peg-IFN- α 2b (1.5 μ g/kg weekly s.c.) and ribavirin (1,200 mg/day) was started. Six weeks later she had begun to complain of fluctuating symptoms of malaise, fatigue and nasal speech followed by generalized weakness. IFN treatment was discontinued and she was admitted to the hospital. At neurological examination ptosis of the right eye, difficulty in mastication and swallowing, and mild proximal weakness of the limbs were found. MG was

diagnosed on the basis of prostigmin testing, decrement of the third compound muscle action potential on repetitive nerve stimulation, and positive anti-AchR antibody titer (31 nmol/l). Cranial magnetic resonance imaging and thoraco-abdomino-pelvic computerized tomography were reported to be normal.

Pyridostigmine was given six times a day and treatment with intravenous immunoglobulin (0.4 g/kg daily i.v.) was given for 3 days only. The symptoms resolved under this treatment. The patient had been receiving pyridostigmine for the last 3 years, but recently she was admitted to the outpatient clinic for follow-up after complaining of continuous fatigue. Laboratory examinations revealed high levels of ALT, HCV RNA and acetylcholine receptor antibodies.

In the current literature, development of MG has been reported in cases with untreated hepatitis C and in those who were treated with small or high doses of IFN for CHC [7–9]. Myasthenic crises have also been reported during treatment of CHC by IFN in MG patients [4]. The pathogenesis is not fully understood because of the complex immunological effects of IFNs, including enhanced lymphocyte cytotoxicity, inhibition of T suppressor cell function, increased expression of major histocompatibility complex (MHC) class I antigens, production of proinflammatory cyto-

kines, and differentiation of antigen-presenting cell activation of T helper lymphocytes by autoantigens. Some or all of them might contribute to the development of autoimmune disease [6]. In this case, the patient had no signs of MG or other autoimmune disease before the IFN treatment. IFN and ribavirin combination therapy are the preferred treatment of choice in CHC. Autoimmune diseases are not frequently developed in patients with CHC treated with ribavirin and IFN. Development of MG due to a standard dose of combination therapy with IFN- α and ribavirin have been reported previously in 2 patients [3, 6].

In the literature it has been reported that MG due to IFN therapy begins 6 weeks to 3 months after the beginning of treatment [3, 8]. In our case, symptoms started 6 weeks after the beginning of the treatment. Before the treatment, she had not been suffering from symptoms such as malaise, dysphagia, ptosis and generalized weakness.

In conclusion, during interferon plus ribavirin combination treatment in patients with CHC, although rare, myasthenia gravis has been observed. Patients with CHC should be followed with special attention given to autoimmune diseases both before and after the treatment.

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