Clinical Overlap of Multiple Sclerosis and Autoimmune Hepatitis: Three Cases

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ABSTRACT
Multiple sclerosis (MS) is an autoimmune, inflammatory disease characterized by demyelination and axonal degeneration in the central nervous system (CNS).1 Autoimmune hepatitis (AH) is a chronic disease characterized by hypergammaglobulinemia, high levels of transaminases, presence of antibodies, and histologically by the necroinflammatory process with interface hepatitis.2 MS may be associated with AH, type 1 diabetes mellitus (DM), and autoimmune thyroiditis (AT).1 In literature, 8 cases with overlap of MS and AH have been reported. In this report, we present 3 cases which were detected with overlap of MS and AH, and are very rare condition in literature.

Key Words: Multiple sclerosis. Autoimmune hepatitis. Autoimmune diseases.

INTRODUCTION
Multiple sclerosis (MS) is an autoimmune, inflammatory disease characterized by demyelination and axonal degeneration in the central nervous system (CNS).1 Autoimmune hepatitis (AH) is a chronic disease characterized by hypergammaglobulinemia, high levels of transaminases, presence of antibodies, and histologically by the necroinflammatory process with interface hepatitis.2 MS may be associated with AH, type 1 diabetes mellitus (DM), and autoimmune thyroiditis (AT).1 In literature, 8 cases with overlap of MS and AH have been reported. In this report, we present 3 cases which were detected with overlap of MS and AH, and are very rare condition in literature.

CASE REPORT

Case 1: A 36-year-old woman with a 3-year history of relapsing-remitting MS (RRMS) presented to our clinic with a history of 4 MS attacks. She had been receiving interferon-β-1a treatment for 2 years, and the results of her liver function tests (LFTs): (Alanine transaminase (ALT) = 427 U/L and aspartate transaminase (AST) = 327 U/L) were 10 and 8 times higher than the normal values, respectively. The dose of interferon was reduced to half dose. Fifteen days later, since the LFT parameters were still high, the interferon treatment was terminated; and thus the gastroenterology department was consulted to find out the reasons for abnormally high results. All the tests: Alkaline phosphatase (ALP), total globulin, gammaglobulin, immunoglobulin G (IgG), antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), liver kidney microsomal antibody (anti-LKM1), hepatitis markers, anti-soluble liver antigen autoantibody (anti-SLA), liver pancreas antibody (LP), anti-liver cytosolic antigen type 1 (LC1), asialoglycoprotein receptor 1 antibody (ASGPR), human leukocyte antigen (HLA) DR3-DR4, viral serological tests, brucellosis, Salmonella, hemochromatosis, and the tests for Wilson’s disease) were requested. All the test results were normal and hepatobiliary pathology was not detected in abdominal ultrasonography (USG). Liver biopsy indicated the presence of AH. However, no positive family history was found and the systemic examination was normal. In neurological examination, optic atrophy was detected in the right eye, deep tendon reflexes (DTRs) were hyperactive, tandem gait test was poor, and other results were normal. In the visual evoked potential (VEP) test, the P100 wave latencies in the right and left eyes were 140 msn and 138 msn, respectively. Cranial magnetic resonance imaging (MRI) showed peri-supraventricular white matter and in the right cerebellar hemisphere and vertically oriented plates corpus callosum. Intravenous (IV) contrast was used. The patient was given corticosteroid (CS) 30 mg and azathioprine (AZT) 50 mg, which were gradually increased to 125 mg/day. In the follow-up period, the patient is currently in the remitting phase.

Case 2: A 38-year-old woman with a 10-year history of AH presented to our clinic with no history of pathologies.
Hepatobiliary USG was normal and the diagnosis of AH was established by liver biopsy. The patient was receiving AZT 50 mg/day at presentation. She was referred to the neurology clinic due to numbness and loss of strength in her left arm and leg and face. In the neurological examination, the muscle strength was 4/5 in the left upper and lower extremities, left hemihypesthesia was detected, DTRs were hyperactive, and tandem gait test was poor. The patient had a positive family history of MS. In the VEP test, the P100 wave latencies in the right and left eyes were 122 msn and 116 msn, respectively. In cranial MRI, high signal intensity was detected in vertically oriented T2-weighted and FLAIR sequences in the peri-supraventricular white matter and IV contrast was absent. Following the confirmation of the diagnosis of MS, methylprednisolone 1 g/day was administered for 5 days. The AZT dose was increased to 100 mg/day. The patient clinically improved in the follow-up period.

Case 3: A 45-year-old woman with a 3-month history of RRMS was detected with elevated LFT parameters during her follow-up visit for interferon β1a treatment. Fundus examination revealed a temporal paleness in the right eye and right hemihypesthesia. The patient had a 3-year history of hypertension. The elevated LFT parameters (ALT: 165 U/L, AST: 267 U/L) were considered to be associated with the interferon β1a treatment; therefore, the dosage of interferon was reduced to half dose. At the follow-up visit on day 15, the interferon β1a treatment was terminated since no reduction was observed in the LFT parameters. Due to the continuing neurological complaints, fingolimod therapy was started and a consultation was made with the gastroenterologist due to the elevated LFT parameters. All the tests were normal and the diagnosis of AH was established by liver biopsy. Cranial MRI revealed hyperintense foci on T2-weighted and FLAIR sequences with sparse projections that were vertically oriented to the corpus callosum in bilateral white matter. The MRI also revealed diffuse hyperintense signal areas in the corpus callosum, high signal intensity in the calloso-septal interface, and multiple patchy areas of increased signal intensity on T2 sagittal images and IV contrast was present. In the VEP test, bilateral P100 wave latency was remarkably long (120 msn). The patient has been in the remitting phase both for MS and AH for the last 6 months.

**DISCUSSION**

MS is a chronic disease characterized by demyelination and axonal degeneration in the CNS. Definitive diagnosis of AH is based on a number of criteria including gender, alcohol abuse, viral serology, use of hepatotoxic drugs, positive autoantibodies (ANA, ASMA, Anti-LKM, SLA/LP), elevated immunoglobulin levels, ALP/aminotransferase ratio, family history, hepatotropic virus infections, blood transfusion, Wilson's disease, α-1 antitrypsin deficiency, hemochromatosis, history of biliary tract disorders, liver biopsy, and absence of clinical symptoms.

Positive autoantibodies have been reported in AH patients with varying degrees and the patients with AH Type I are mostly positive for ANA and ASMA, the ones with AH Type II are positive for LKM-1, and those with AH Type III are positive for SLA/LP. The immunological indicators needed for the subclassification of AH patients were not present in some patients and thus they were classified as the AH patients negative for autoantibodies.

Autoimmune diseases (ADs) arise from the antigens that are developed as a response to pathologic reaction and from immunodeficiency characterized by an insufficiency of defining their target antigens. Overlap of MS with other AD, such as systemic lupus erythematosus, rheumatoid arthritis, chronic active hepatitis, type 1 DM, uveitis, pemphigus, psoriasis, Crohn's disease, inflammatory intestinal disease, anemia, and AT has been reported in several studies.

De Seze et al. reviewed 1.800 MS patients and reported 3 cases with overlap of MS and AH. The study reported the overall incidence of AH as 0.17, which was much higher than the incidence in general population (~0.0169%). The authors also suggested that performing liver biopsy is of prime importance in the patients with elevated LFT parameters and no history of treatment.

Another study reported 8 MS patients with liver injury following interferon β treatment. All the patients were white women and their mean age was 49 years. Mean ALT level was 725 ±593 U/L, and all the complaints were acute in onset. The study concluded that interferon β hepatotoxicity mostly affects women and has a variable time to onset, and this condition can also arise from adverse drug reaction.

A study presented a 61-year-old woman with untreated co-existence of MS and AT, who presented with pain in the right upper quadrant and then diagnosed as AH depending on clinical and laboratory findings and clinically improved following AZT and CS treatment. The authors also suggested that the prevalence of AH in patients seems to be higher in patients with MS than in the general population and recommended that attention should be paid to determine whether AH occurs after interferon β or CS treatment in patients with MS or even in untreated MS patients? Another case report revealed that the liver function impairment, caused by interferon β-1a, can be delayed for 5 years after starting treatment and this can be an idiosyncratic reaction. The study also suggested that liver functions should be regularly monitored in patients with MS who receive interferon β even after the first 6 months of treatment, particularly in the patients receiving liver-toxic medications.
In our patients, Case 1 had been receiving interferon for the last 2 years and had not received any other liver-toxic medications. In Case 3, the complaints of the patient had started 3 months after the use of interferon. Case 2 had no history of use of interferon. We also consider that this situation is an idiosyncratic reaction.

In conclusion, the overlap of MS and AH is a very rare condition. This condition should be further investigated in multicenter studies with large series.

REFERENCES


