Coexistence of primary sclerosing cholangitis in a patient with myasthenia gravis

P. J. Lorenzoni, R. H. Scola, C. S. K. Kay, D. A. Muzzillo[1], L. C. Werneck

Neurology Division, [1]Gastroenterology Division, Department of Internal Medicine, Federal University of Paraná, Curitiba PR, Brazil

Abstract

Myasthenia gravis (MG) is an immune-mediated disease that compromises the postsynaptic membrane of the neuromuscular junction. Primary sclerosing cholangitis (PSC) is considered an immune-mediated cholestatic liver disease. Both MG and PSC include an autoimmune pathogenesis, so there is some evidence that patients with MG or PSC have a higher risk of developing autoantibodies and other immune disorders than normal controls, but the coexistence of these two disorders has never been documented. We report a 40-year-old woman who presented with MG when she was 20 years old and developed PSC 20 years after a thymectomy. Liver biochemistry revealed cholestasis. Magnetic resonance imaging showed multifocal strictures and beads involving the intrahepatic bile ducts. A liver biopsy confirmed sclerosing cholangitis. Serological analysis demonstrated positive autoantibodies (Anti-nuclear antibodies, anti-smooth muscle antibodies). Repetitive stimulation had a decremental response, and antibodies to acetylcholine receptors were detectable. To our knowledge, this is the first case of PSC in a patient with MG. The main characteristics of both MG and PSC combination are discussed.

Key Words

Autoimmune diseases, myasthenia gravis, sclerosing cholangitis, thymectomy

For correspondence:
Dr. Rosana Herminia Scola, Serviço de Neurologia, Hospital de Clínicas da UFPR, Rua General Carneiro 181/3º andar, 80060-900 Curitiba PR, Brazil. E-mail: scola@hc.ufpr.br

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Introduction

Myasthenia gravis (MG) is an immune-mediated disease that compromises the postsynaptic membrane of the neuromuscular junction and usually leads to symptoms of fatigability and decreased muscle strength.[1] Primary sclerosing cholangitis (PSC) is considered an immune-mediated cholestatic liver disease that is characterized by diffuse inflammation and fibrosis of the intra- and extrahepatic bile ducts.[2-4]

Both these diseases have been found to be associated with a large number of other autoimmune diseases, but coexistence of MG and PSC has not yet been documented.[2,3,5-9]

We report the first known case of PSC in a patient with MG.

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Case Report

A 20-year-old woman presented with intermittent diplopia, a mild limitation of ocular movements, progressive palpebral ptosis, and weakness that increased during periods of activity and improved after periods of rest. A neurological examination showed a limitation of ocular movements, bilateral palpebral ptosis, and mild paresis of both arms and legs (Medical Research Council grade 4). A recording of compound muscle action potentials demonstrated an abnormal decrement in response that was greater than 10% during repetitive stimulation of the ulnar and facial nerves. The diagnosis of MG was made, and after treatment with pyridostigmine, prednisone, and thymectomy, the disease was controlled.

At 40 years of age, the patient developed a progressive pruritus, jaundice, fever, anorexia, nausea, weight loss, and steatorrhea. The physical examination disclosed marked jaundice and mild hepatomegaly. Serum bilirubin, aspartate aminotransferase, alanine transferase, and alkaline phosphatase levels were elevated. The albumin level and prothrombin time were normal. Hepatotoxicity was ruled out. CMV, EBV, HAV, HBV, HCV, and HIV serological tests were negative. Anti-nuclear antibodies (ANA: 1/640) and anti-smooth muscle antibodies (SMA: 1/20) were detectable, but no anti-neutrophil cytoplasmatic antibody, liver kidney microsomal type 1 antibody, or anti-

mitochondrial antibody was present. Magnetic resonance cholangiopancreatography detected a multifocal stricture and bead involving the intrahepatic bile ducts. Liver biopsy changes were consistent with sclerosing cholangitis with moderate cholestasis. The diagnosis of PSC was made, and treatment with ursodeoxycholic acid was added, which resulted in a partial improvement of the cholestatic biochemistry, but not in the cholestatic symptoms.

At that time, she also presented a worsening of her MG symptoms (diplopia and weakness). The neurological examination showed a persistence of the limitation of ocular movements, bilateral palpebral ptosis, and mild paresis of both arms and legs (MRC grade 4). MG investigation found positive anti-acetylcholine receptor antibody serostatus (7.46 nmol/l; normal, <0.15 nmol/l) and an abnormal decrement response greater than 10% during repetitive stimulation of the median, ulnar, and facial nerves. The MG management with pyridostigmine and prednisone controlled her disease. All studies were done following informed consent.

Discussion

There is evidence that patients with MG or PSC have a higher risk of developing autoantibodies and other autoimmune disorders than normal controls do.[2,6-11] Clinical and serological findings of concomitant autoimmunity have been described in 25 to 70% of PSC patients and in up to 20% of MG patients, but a coexistence of these two conditions, as seen in our patient, has never been documented.[2,5-11]

MG is mediated by autoantibodies against the acetylcholine receptors in the postsynaptic membrane which compromises neuromuscular transmission.[1] This highly specific antibody is present in about 80% of MG patients, and the remaining cases are associated with antibodies targeting other specific proteins in the postsynaptic membrane.[1,7]

The etiology of PSC remains unknown; among the many pathogenic theories formulated, the most important causes are associated with genetic, autoimmune, and inflammatory diseases triggered by infectious agents.[2,4] The hypothesis of PSC as an autoimmune disease is supported by the high frequency of inflammatory bowel disease in PSC patients, the increased incidence of other coexisting autoimmune diseases, and the presence of multiple autoantibodies.[2-4,9-11] No antibody is specific for PSC.[10,11] As many as 90% of patients with PSC have at least one detectable autoantibody; however, the presence of multiple antibodies does not correlate with disease activity.[10,11] ANA and SMA antibodies are found in up to 60% of patients with PSC [10,11] The main autoimmune disease associated with PSC is inflammatory bowel disease, especially ulcerative colitis, which occurs in up to 75% of PSC patients, but several other autoimmune disorders have been reported to be associated in up to 25% of cases.[2-4,9]

Autoimmune hepatitis repeatedly has been documented in association with PSC and primary biliary cirrhosis.[12] In addition, MG has previously been reported in patients with primary biliary cirrhosis and autoimmune hepatitis, which suggest that a coexistence with PSC also could be possible in MG patients.[13,14] In this case, the coexistence of MG with the presence of serum antibodies sustains the autoimmune theory a possible etiology for PSC. However, the exact role of immune system impairment in the development, behavior, and progression of the disease is not still completely understood.

MG patients who undergo thymectomy have a higher incidence of other autoimmune disorders. The response to thymectomy in MG patients with or without an associated autoimmune disease is similar even if the second autoimmune disease had begun before the thymectomy.[8] However in this patient, the thymectomy was performed almost 20 years before PSC presentation. A thymectomy abolishes the induction of tolerance afforded by the oral administration of myelin basic protein in experimental autoimmune encephalomyelitis in adult mice, probably due to the failure to generate suppressor T-cells, causing exacerbated B-cells activity.[15] Active PSC in MG patients with previous thymectomy may represent a breakdown of self-tolerance by similar mechanisms.

We speculate that a nonspecific immune dysregulation could promote the development of PSC in a subgroup of patients with MG who have a specific genetic background that contributes to the immunologic pathogenesis of PSC or induced by thymectomy, but further studies are needed to clarify the exact relationship between the two conditions.

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