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Concurrence of Multifocal Motor Neuropathy and Hashimoto's Thyroiditis

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Background Multifocal motor neuropathy (MMN) is an immune-mediated disorder that is characterized by slowly progressive and asymmetrical weakness, but its pathophysiological mechanism is uncertain. The hypothesis that MMN is an immunological disease has been supported by the proven therapeutic effects of intravenous immunoglobulin and the detection of antiganglioside antibodies in MMN patients. The coexistence of MMN with other immune diseases has been rarely reported.

Case Report A 37-year-old woman visited our hospital complaining of weakness in both hands. The clinical manifestations coincided well with MMN: predominantly distal upper-limb weakness, asymmetric involvement, a progressive course, absence of sensory symptoms, absence of pyramidal signs, and sparing of the cranial muscles. The electrophysiological findings also supported a diagnosis of MMN, with motor nerve conduction block in the median, ulnar, and radial nerves, without sensory nerve involvement. The patient was simultaneously diagnosed as having Hashimoto's thyroiditis, which is a well-known immune-mediated disease.

Conclusions The concurrence of MMN and Hashimoto's thyroiditis in our patient is significant for understanding the immunological characteristics of the two diseases.

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Key Words multifocal motor neuropathy, hashimoto's thyroiditis, MMN.

Introduction

Multifocal motor neuropathy (MMN) is an immune-mediated disorder with predominantly distal, mainly upper limb, asymmetrical manifestations, and pure motor neuropathy.¹⁻³ The hallmark of MMN is the presence of conduction block in motor nerve conduction studies (NCSs). MMN is a treatable disorder, with about 80% of patients responding to intravenous immunoglobulin.^{2,4} For this reason, it needs to be distinguished from motor neuron disease, which is much more common but remains

untreatable. The pathogenesis of the disease is still unknown, but there is some evidence, based mainly on the clinical improvement of patients after immunological treatments, that MMN is related to an immune disorders.³ MMN is also frequently associated with antiganglioside antibodies to monosialoganglioside (GM1), and disialoganglioside (GD1b) of the IgM type.⁵ Gangliosides are sialic acids containing glycosphingolipids that are particularly abundant in the neural membranes of the nervous system; they are also detected in thyroid cells.^{3,5,6} Antibodies against the main gangliosides, such as GM1 and GD1b, are found in patients with MMN, which suggests an autoimmune pathogenic mechanism.

Hashimoto's thyroiditis is one of the most frequent causes of primary hypothyroidism and a well-known immune-associated disease; circulating thyroid autoantibodies are usually detect-

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ed.⁷ The histopathologic findings of Hashimoto's disease show widespread lymphocyte infiltration in the thyroid tissue.⁸ Other autoimmune diseases may also occur in patients with Hashimoto's disease.⁹ However, the coincidence of MMN and Hashimoto's thyroiditis has rarely been reported, and the pathophysiology has been limitedly clarified.

We report herein an unusual case of MMN accompanied simultaneously by Hashimoto's thyroiditis.

Case Report

A 37-year-old woman visited our hospital complaining of weakness in both hands. Five years prior to admission, she had noticed mild weakness of insidious onset in her left hand. However, she did not undergo medical treatment or visit clinics. Weakness developed in her right hand 2 years later. The weakness in both hands progressed gradually and the severity increased. She began to experience difficulty in writing, handling chopsticks, and making a fist. The patient visited local clinics, but was not sufficiently evaluated. On admission the patient had severe weakness and muscle atrophy in both hands, without sensory change. Her past medical history and the antenatal and postnatal periods had been uneventful. She had attended school and had led an apparently normal life until she noticed neurological manifestations. Relevant diseases, a familial history of neurological disease, smoking, and alcohol were not noted. She had taken an antihypertension drug and oral thyroid hormone at a local clinic. On examination, her vitals sign were stable, with a blood pressure of 140/90 mmHg and a heart rate of 72 beats/min. A neurological examination revealed that she was alert and her orientation was intact. Cognitive impairment was not detected. There were no abnormal findings on cranial nerve examination.

Motor system examinations using the Medical Research Council (MRC) grade revealed severe motor weakness in both hands (flexor pollicis longus, MRC grades 3/5 and 2/5 on the right and left, respectively; flexor digitorum profundus and sublimis, MRC grades 3/5 and 3/5; flexor carpi ulnaris and radialis, MRC grades 3/5 and 3/5; extensor pollicis brevis and longus, MRC grades 3/5 and 2/5; extensor carpi radialis, MRC grade 3/5 and 2/5; extensor carpi ulnaris, MRC grades 3/5 and 3/5; extensor digi-

torum communis, MRC grades 2/5 and 2/5; abductor pollicis brevis, MRC grades 3/5 and 3/5; and abductor digiti minimi, MRC grades 2/5 and 2/5). Prominent muscle atrophy and deformities were observed distally in both hands (Fig. 1A). The motor power of both lower extremities was normal. The deep tendon reflex was decreased in the upper extremities.

The patient exhibited symmetric and intact responses to all sensory stimuli, and her cortical senses were intact. Her neck was supple, no carotid bruit was audible, and the results of a cerebellar function test were normal.

Laboratory investigations revealed a normal hemogram, serum electrolytes, and renal function. Cerebrospinal fluid findings were normal. Evaluations for vasculitis involving rheumatoid factor, anti-dsDNA antibody, lupus anticoagulant, anticardiolipin antibody, antithrombin III, antineutrophil cytoplasmic antibody, anti-SSA and SSB (Sjogren syndrome A and B) antibody, complement 3/4, anti-jo-1 antibody, cryoglobulin, immunofixation electrophoresis/protein electrophoresis, anti-GM1 antibody, and anti-GD1b antibody were within the normal range or negative, with the exception of a mildly elevated fluorescent antinuclear antibody titer (1 : 40). The results of tumor screening tests involving alpha-fetoprotein, carcinoembryonic antigen, cancer antigen (CA)-19-9, and CA-125 were normal. Hexosaminidases A and B, and creatine kinase were also within the normal ranges. However, a thyroid function test revealed an abnormally elevated antithyroglobulin antibody titer (794 U/mL, normal range: 0-100 U/mL) and antimicrosomal antibody (26,030 U/mL, normal range: 0-100 U/mL), but the thyroid hormone levels, including T3, free T4, and thyroid stimulating hormone, were normal.

Cervical magnetic resonance imaging revealed no prominent abnormalities except mild disc protrusion at the C5-6 and C6-7 levels. NCSs and electromyography were performed using standard techniques of percutaneous supramaximal stimulation and recordings. These examinations revealed motor neuropathies in the median motor nerve, ulnar motor nerve, and radial motor nerve, with definite motor conduction block manifesting as the compound muscle action potential amplitude being more than 50% lower for proximal than for distal stimulation across a standard peripheral nerve segment (Fig. 2). However, the findings of sensory NCSs in the upper extremities, and motor and sen-

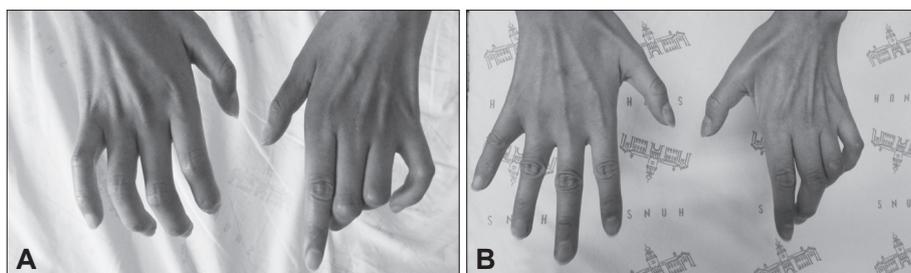


Fig. 1. Deformities of both hands in our patient. Severe deformities in the right hand (A) were much improved (B) after treatment with high-dose intravenous immunoglobulin (0.4 g/kg/day) for 5 consecutive days.

sory NCSs in the lower extremities were normal. Thus, even though the patient was negative for antiganglioside antibodies, the electrophysiological study and clinical manifestations resulted in a diagnosis of MMN.

A biopsy of the patient's thyroid tissue by ultrasound-guided

aspiration revealed diffuse lymphocyte infiltration, a finding that is consistent with Hashimoto's thyroiditis (Fig. 3). She was treated with high-dose intravenous immunoglobulin (0.4 g/kg/day) for 5 consecutive days and then discharged. When she visited our Outpatient Department 1 month later, the weakness and

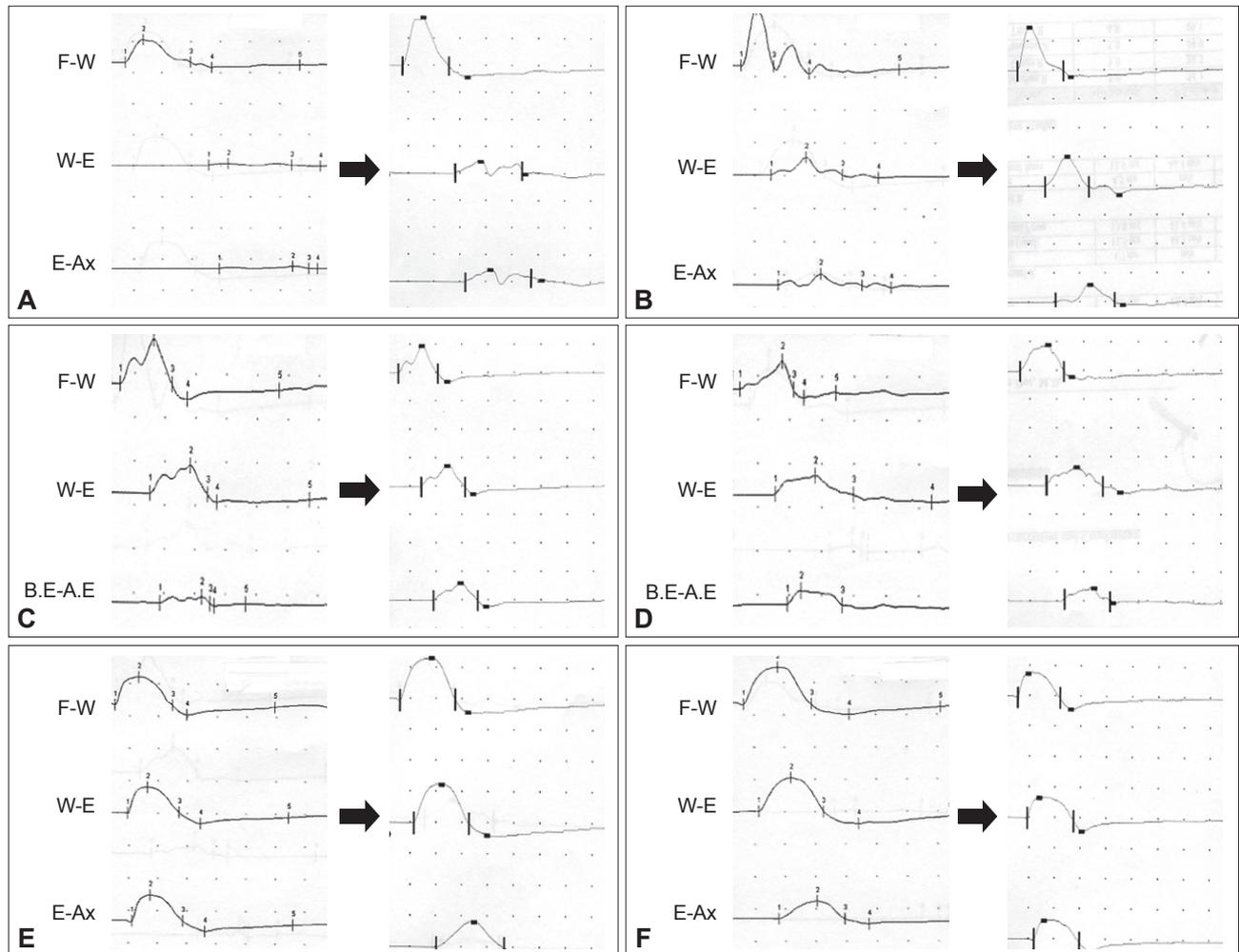


Fig. 2. Raw data of nerve conduction studies (NCSs) of the patient's right median motor nerve (A), left median motor nerve (B), right ulnar motor nerve (C), left ulnar motor nerve (D), right radial motor nerve (E), and left radial motor nerve (F). The raw data shown on the left and right sides of the arrow correspond to before and after treatment, respectively. Before intravenous immunoglobulin therapy, the NCSs revealed conduction block in right median motor nerve, left median motor nerve, right ulnar motor nerve, left ulnar motor nerve and left radial nerve. One month later, after high-dose intravenous immunoglobulin therapy, conduction blocks were improved, especially for the left median motor nerve, right ulnar motor nerve, and left radial motor nerve. F-W: finger-wrist, W-E: wrist-elbow, E-Ax: elbow-axilla, W-B.E: wrist-below elbow, B.E-A.E: below elbow-above elbow, A.E-Ax: above elbow-axilla.

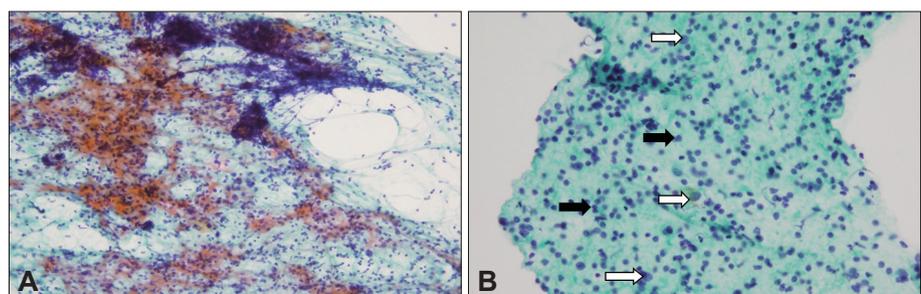


Fig. 3. Microscopy findings of a biopsy sample of the patient's thyroid tissue reveal diffuse lymphocyte infiltration (black arrows) and a few sheets of follicular epithelial cells (white arrows) without malignant cells (Papanicolaou staining: A, $\times 200$; B, $\times 400$).

deformity in her right hand was considerably improved (Fig. 1B) and the conduction block of the motor nerves were mildly improved, as evaluated by follow-up NCSs (Fig. 2). This patient will be continuously followed up at the Outpatient Department.

Discussion

The case presented herein is characterized by an association between MMN and Hashimoto's thyroiditis. The clinical presentation was typical for MMN, since such patients complain predominantly of progressively worsening upper-limb weakness (mainly distal), asymmetric involvement, absence of sensory symptoms, absence of pyramidal signs, and sparing of the cranial muscles.^{1,2} The electrophysiological findings also supported a diagnosis of MMN, with motor nerve conduction block in the median, ulnar, and radial nerves, without sensory nerve involvement.

The most important investigations for determining MMN are electrophysiological studies, and in particular motor NCSs, for which the main finding in MMN is a persistent multifocal conduction block.^{1,2,5} Conduction block manifests as a lower compound muscle action potential amplitude or a smaller area on electrical stimulation of a nerve at a proximal site, compared to a distal site. Although conduction block is characteristic of MMN, it may be found in several other disorders such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and nerve ischemia.^{10,15} Therefore, the appropriate interpretation of a conduction block also requires consideration of the clinical presentation.¹⁰ Our patient could be clinically differentiated from Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and nerve ischemia since she complained of slowly progressing, asymmetric motor weakness in the distal upper extremity, without sensory symptoms. According to the clinical manifestations, electrophysiological study findings, and response to intravenous immunoglobulin, a diagnosis of MMN in our patient was reasonable, although she was negative for antiganglioside antibodies related to MMN. Elevated antiganglioside antibody titers are a typical finding; however, the sensitivity of this measure is uncertain, reportedly varying between 30% and 80% (although usually lying between 40% and 50%).^{1,2,5} In addition, these antibodies are not specific for MMN, having been found in about 10% of cases of the pure lower motor neuron variant of motor neuron disease.⁵ Therefore, the negative antiganglioside antibody finding did not rule out a diagnosis of MMN in the case reported here.

The pathophysiology of MMN is believed to be focal motor nerve demyelination, resulting in conduction block. However, this remains uncertain, and an immune-mediated origin of MMN is suspected on the basis of the presence of antiganglioside antibodies and response to immune intervention. The ganglioside

GM1, which is abundant in motor nerves at the nodes of Ranvier and motor end plates, may be the target of an immune response, resulting in conduction block.^{3,5} *In vivo* and *in vitro* experiments have demonstrated that the serum from patients with MMN and anti-GM1 antibodies induces focal conduction block after intraneural injection.¹¹ Disruption of the blood-nerve barrier by these antibodies has also been hypothesized as a possible mechanism.¹² However, about 50% of reported cases of MMN are negative for anti-GM1 antibodies.⁵ Despite a probable autoimmune basis, the precise mechanism underlying the development of MMN is still poorly understood.

On admission to our hospital, our patient was additionally diagnosed as having Hashimoto's thyroiditis, which is a well-known autoimmune disease and one of the most frequent causes of primary hypothyroidism. The prevalence of various diseases with autoimmune components in patients with Hashimoto's thyroiditis and in their relatives is higher than can be accounted for by chance.⁷⁻⁹ The plasma membranes of thyrocytes are also very rich in ganglioside, and these are particularly abundant in neural membranes, inducing specific antibodies for MMN.^{6,13} The high concentrations of gangliosides in both neural and thyroid tissues had led to some authors suggesting a pathogenic relationship between MMN and Hashimoto's thyroiditis and a potential immunological interaction between antiganglioside antibodies and both neural and thyroid tissues.¹⁴ Unfortunately, antiganglioside antibodies were not detected in our case.

The reported variations in the prevalence of these antibodies in MMN have been variably attributed to technical differences in the procedures adopted by different laboratories, differences in the controls used to establish normal reference values, and differences in the disease period tested for MMN. The reasons for such a wide variation in the percentage of abnormal findings remain to be elucidated.

MMN is a rarely described, treatable, immune-mediated motor nerve disease; however, there are many remaining uncertainties about the precise underlying pathophysiological mechanisms. Therefore, the case reported here is significant in that it demonstrates a possible link and pathophysiological mechanism between MMN and a more common autoimmune disease, Hashimoto's thyroiditis.

Conflicts of Interest

The authors have no financial conflicts of interest.

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