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Clinical Observations

Childhood-Onset Multifocal Motor Neuropathy With Immunoglobulin M Antibodies to Gangliosides GM1 and GM2: A Case Report and Review of the Literature

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ABSTRACT

Multifocal motor neuropathy is a rare immune-mediated neuropathy characterized by progressive asymmetric weakness and atrophy without sensory abnormalities. Although disease onset is usually in adulthood, a few childhood-onset cases have been reported. Here, we report the case of an 8-year-old boy with multifocal motor neuropathy who presented with a slowly progressive left and distal upper limb weakness without sensory loss. The initial high-dose intravenous immunoglobulin treatment significantly improved left upper limb muscle weakness. Continued monthly intravenous immunoglobulin treatment gradually improved muscle strength for several months initially. While the muscle strength decreased slightly after 8 months of therapy, it was better than that before intravenous immunoglobulin treatment. One year and eight months after the initiation of treatment, serum testing for IgM antibodies to gangliosides, GM1 and GM2, was negative. This is the first pediatric report of the serum IgM autoantibodies positive to GM1 and GM2. The clinical course is similar to that of partial intravenous immunoglobulin responders among patients with adulthood-onset multifocal motor neuropathy. Since the symptoms plateaued after the initial intravenous immunoglobulin therapy, prognosis appears to be determined by the patient's initial response to intravenous immunoglobulin treatment.

Keywords: immune-mediated neuropathy, multifocal motor neuropathy, muscle atrophy, anti-ganglioside antibodies, intravenous immunoglobulin

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Introduction

Multifocal motor neuropathy (MMN) is a chronic demyelinating peripheral motor nerve disease characterized by a slow and progressive asymmetrical muscle weakness.[1,2] MMN is rare and occurs commonly in adults. Pediatric cases of MMN are extremely rare, of which only three cases have been previously reported.[3-5] The pathologic mechanisms of MMN are not clear, although immunoglobulin (Ig) M autoantibodies against the ganglioside GM1 may possibly attack the nodes of Ranvier and change their structure.[1,2] Patients who test positive for the GM1 IgM antibody represent approximately half of those with MMN,[6,7] and therefore this antibody may be useful for the diagnosis of MMN.[8] MMN is treatable with intravenous Ig (IVIg), and its continuous administration is required for most cases. However, for a majority of patients with MMN, muscle strength decreases gradually despite continued IVIg treatment.[9,10] Because the clinical course of childhood-onset MMN is not well understood, we report a case positive for GM1 and GM2 IgM antibodies that received IVIg treatment for one year and eight months. We also compared

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this patient to the typical clinical course for adulthood-onset MMN and reviewed the previously reported examples of childhood-onset MMN.

Patient Description

This 8-year-old Japanese boy was referred for evaluation and treatment of left arm muscle weakness and atrophy. He was born at term to nonconsanguineous parents and had no family history of neurological disease. His past history was unremarkable, and he had not received immunizations for several months before admission. In the six months before presentation, the child had become unable to grasp or throw a ball with his left arm, and he was unable to hang down from a bar. Four months before admission, he developed drop of the left wrist and thumb. A magnetic resonance imaging (MRI) revealed left brachial plexus nerve swelling.

He was fully conscious. Neurological examination did not show cranial nerve involvement. Reflexes of the left bicep tendon, left triceps, and left brachioradialis were absent. Tongue fasciculations were not observed. Muscle weakness and atrophy of the left arm were evident. The Medical Research Council (MRC) scale of the upper limbs showed distal and dominant left upper limb weakness. The MRC sum score of the 24 muscles of his left upper limb was assessed (Table 1). The grip and pinch dynamometer revealed the reduction of the left grip and pinch powers. Sensory impairment was not found.

Blood cell counts and blood biochemistry were normal. Serum erythrocyte sedimentation rate, C-reactive protein, and complement and double-strand DNA antibody were negative and serologic, and culture evidence of specific infection such as cytomegalovirus, varicella-zoster virus, mumps virus, and mycoplasma were also negative. Cerebrospinal fluid cell counts and biochemistry were normal. Oligoclonal band and myelin basic proteins were negative. The IgG index was 0.7. Computed tomography showed severe atrophy of the left distal arm muscles. The T2-weighted MRI scan showed swelling and high signal intensity in the C5 to C7 brachial plexus nerves, and the T1-weighted MRI scan with gadolinium images showed enhancement in the same nerves (Fig 1). Whole-body gallium scintigraphy was normal.

Electrophysiologic assessments revealed that the motor conduction velocities of the right side nerves, left ulnar nerve, left common peroneal nerve, and left tibial nerve were normal, whereas the motor conduction velocity of the left median nerve was reduced to 9.9 m/s, and the distal latency was 5.6 ms (Fig 2). Negative compound muscle action potential area reduction on proximal versus distal stimulation of the left median nerve and the left ulnar nerve were 10.7% and 22.4%, respectively, and met the criteria for conduction block. Compound muscle action potential was not detected by the stimulation of the left radial nerve. Sensory conduction velocities of both sides of upper limb nerves were within normal range (left median nerve 54.2 m/s, right median nerve 56 m/s, left radial nerve 60.0 m/s, right radial nerve 59.8 m/s, left ulnar nerve 46.4 m/s, right ulnar nerve 53.6 m/s).

Electromyography (EMG) of the left bicep muscle revealed neurogenic changes, such as spontaneous potential and positive sharp waves of the fibers, whereas EMG of the left extensor digitorum muscle did not show changes. EMG showed no myogenic changes. The nine kinds of serum antigalactocerebroside IgM and IgG antibodies including GM1, GM2, GM3, GD1a, GD1b, GD3, GT1b, GQ1b, and Gal-C were assessed. Serum antigangliosides GM1 IgM and GM2 IgM antibodies tested positive. Therefore the patient was diagnosed with definite MMN according to the clinical diagnostic criteria by the European Federation of Neurological Societies/Peripheral Nerve Society.[7]

High-dose IVIg (400 mg/kg/day for 5 days) was administered soon after the diagnosis was determined. Treatment lag between the disease onset and the initial IVIg therapy was six months. After the initial IVIg treatment, the MRC score of the 24 muscles of the left upper limb improved from 52 (43%) to 81 (68%). The patient then was able to hold a cup with the affected hand. A monthly high dose of IVIg (1500 to 2000 mg/kg) was continued for one year and eight months. After partial but apparent improvement was achieved by the initial IVIg therapy, muscle strength continued to improve for the following seven months of treatment, and the MRC score further improved to 88 (73%; Fig 3). In spite of the continuation of IVIg therapy for one year and eight months, the MRC score gradually decreased and atrophy of median and radial nerve dominated muscles worsened slightly.

Serum antigangliosides GM1 and GM2 IgM antibodies continued to test positive for the first year of IVIg treatment. The high signal intensity of the lesion at the C5 to C7 level on T2-weighted MRI, with inflammation, remained unchanged for 20 months. Assessment of motor conduction in the left median nerve showed a conduction block. Serum antigangliosides GM1 and GM2 IgM antibodies analyzed at one year and four months after the initial treatment of IVIg were negative. The MRC score at this time was 64 (53%).

Discussion

MMN is an acquired, chronic, and demyelinating peripheral motor nerve neuropathy without sensory involvement.[1,2] MMN is rare and reported to have a prevalence of approximately 0.6 persons per 100,000 (0.05 per 100,000 in Japan). The median age of disease onset is 40 years (ranging between 20 and 50 years).[7] Pediatric patients with MMN are extremely rare, since only three such patients have been previously reported.[3-5]

MMN is an immune-mediated disease with IgM gammopathy, and the presence of the GM1 IgM antibody in serum is a useful tool for the diagnosis of MMN. Of the patients with MMN, 30% to 80% are reported to test positive for serum GM1 IgM antibody, whereas fewer test positive for serum GM2 IgM antibody.[7,11,12] Cats et al.[13] reported that of the 88 adult patients with MMN who were tested, GM2 IgM antibody was detected in the serum of only 6%. Nobile-Orazio et al.[14] reported that the GM1 IgM antibody was detected in 11 of 24 adult patients with MMN, and three of those GM1 IgM positive patients were also positive for the GM1 and GM2 complex antibody. GM1 is more abundantly expressed in the motor neuron and is enriched in the