Myasthenia Gravis with Anti-MuSK Antibody, Showing Progressive Muscular Atrophy without Blepharoptosis

Key words: myasthenia gravis, anti-MuSK antibody, bulbar palsy, muscle atrophy, blepharoptosis

Patients with generalized myasthenia gravis (MG) are commonly diagnosed as having seronegative MG (SNMG) when antibodies to the acetylcholine receptor (AChR) are undetectable in serum. Muscle-specific tyrosine kinase (MuSK) has recently been confirmed as a pathognomonic target in a subset of SNMG cases (1). Here, we report an SNMG patient with anti-MuSK antibody who showed progressive muscular atrophy and weakness, particularly in the bulbar region and upper extremities, without blepharoptosis over a 22-year clinical course.

A 24-year-old woman was admitted to our hospital with a one-year history of fluctuating diplopia and easy fatigability in the upper extremities. The edrophonium chloride test was judged positive because easy fatigability in deltoid muscles quickly improved after the administration. In addition to this finding, the patient showed waning phenomena in the repetitive stimulation test at a frequency of 5 Hz as well as negative results for anti-AChR antibodies in serum. The patient was diagnosed as having SNMG, and was treated with pyridostigmine after total thymectomy, while histopathology showed neither thymoma nor lymphoid follicles in the thymic tissue. Nevertheless, clinical symptoms gradually worsened, and three years later oral prednisolone was started at a dose of 30 mg/day for new symptoms suggestive of bulbar palsy, including dysphagia and dysarthria. These symptoms improved slightly soon after starting oral prednisolone, but easy fatigability in the extremities became gradually worse with the development of muscle atrophy. The dosage of oral prednisolone could not be tapered to less than 15 mg/day due to fluctuating myasthenic symptoms. At age 40, needle electromyography (EMG) showed a decrease in neuromuscular units in all muscles examined and low-amplitude potentials suggestive of myogenic change in the tongue and the sternocleidomastoid and biceps muscles. Single fiber EMG frequently demonstrated an increase in the jitter and sometimes a blocking phenomenon of the impulse. Biopsy was performed in the left biceps muscle, and atrophic fibers of varying size were observed to be scattered over the whole specimen without proliferation of the interstitial tissue, while there were no obvious abnormal findings in special stains for muscle enzymes, including ATPase and NADH-tetrazolium reductase. Immunohistochemical analyses showed no deposition of complement in the endplate and well-preserved AChR.

At age 46, the patient developed respiratory failure following a common cold infection, and was readmitted to our hospital. Physical examination showed peripheral cyanosis in addition to bulbar symptoms, including dysphagia and remarkable nasal voice, and weakness in the extremities and facial muscles without blepharoptosis (Fig. 1A). Muscle atrophy was seen severely in the tongue (Figs. 1B, C and D) and moderately in bilateral upper extremities, particularly in the proximal portion. Laboratory data demonstrated positive inflammatory reactions and severe hypoxemia with hypercapnea, and the anti-MuSK antibody level in serum was 4.40 nmol/l (normal <0.05 nmol/l) (2). Shortly after admission, high-dose intravenous immunoglobulin (IVIg) and antibiotics were started under mechanical ventilatory support with a diagnosis of myasthenic crisis. The patient showed gradual improvement of respiratory failure in parallel with a decrease in inflammatory reactions, and adequate oxygenation could be maintained without mechanical ventilatory support approximately 1 month after admission. However, there were no apparent improvements in muscle weakness in the extremities or bulbar palsy even after starting tacrolimus. The patient was discharged from our hospital with administration of prednisolone and tacrolimus at 20 mg/day and 3 mg/day, respectively.

This patient showed a clinical picture typical of SNMG with anti-MuSK antibody, which was characterized by predominant involvement of bulbar muscles and poor therapeutic effectiveness of conventional treatments, including thymectomy (3–6). Bulbar palsy slightly improved after starting oral prednisolone, but thymectomy did not provide the patient with any therapeutic benefits. Myasthenic crisis occurs frequently in this type of MG following infection, resulting in respiratory failure temporarily requiring mechanical ventilatory support as in this patient (5, 6). To quickly reduce serum levels of the anti-MuSK antibody, plasmapheresis is often employed in such an emergency state, but in this patient IVIg was selected as the next therapeutic option because of procedural ease and safety.

The most characteristic point in this patient was muscle atrophy, especially in the tongue and upper extremities, and the lack of blepharoptosis throughout the clinical course. Even in myasthenic crisis, this patient showed no blepharoptosis. Although severe muscle atrophy is sometimes seen in SNMG patients with anti-MuSK antibody (3, 6), the precise pathogenetic mechanism remains unclear. One hypothesis is that poor response to conventional treatments produces disuse atrophy of muscles over a long clinical course, but this patient showed muscle atrophy from a relatively early phase.
of illness. Alternatively, the anti-MuSK antibody itself may cause muscle atrophy. This antibody suppresses cluster formation of AChR after binding to the ectodomain of MuSK (1), and might induce muscle atrophy. Considering that atrophic fibers and myogenic change were seen in the biopsy and needle EMG, respectively, some factors as mentioned above might be related to the development of muscle atrophy in this patient. SNMG with the anti-MuSK antibody should be considered a possible diagnosis in patients showing muscle atrophy in addition to myasthenic symptoms.

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References


Figure 1. The patient showed no blepharoptosis even in myasthenic crisis (A) but severe atrophy was observed in the tongue (B), which was also confirmed on sagittal (C) and frontal (D) sections by magnetic resonance imaging.