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Case Report

Coexistence of Amyotrophic Lateral Sclerosis and Myasthenia Gravis

Satoshi Yamashita[a,*], Akiko Fujimoto[a], Yukiko Mori[a], Tomoo Hirahara[a], Akira Mori[a], Teruyuki Hirano[a,b], Yasushi Maeda[a], Makoto Uchino[a] and Yukio Ando[a]
[a]*Department of Neurology, Graduate School of Medical Sciences, Kumamoto University, Honjo, Kumamoto, Japan*
[b]*Department of Internal Medicine 3rd, Faculty of Medicine, Oita University, Idaigaoka, Hasama, Yufu, Japan*

Abstract. The mechanisms by which amyotrophic lateral sclerosis (ALS) causes motor neuron degeneration remain unknown. We present the case of a 77-year-old Japanese female with clinically probable ALS, who developed ALS symptoms 41 years after onset of myasthenia gravis (MG). We concluded that neither the relapse of MG nor the adverse effects of anti-cholinesterase medication aggravated her symptoms. Although MG and ALS are extremely rare, we reviewed several case reports describing their coexistence. We suggest that clinicians should consider the possibility of ALS occurring with MG. Further investigations will improve our understanding of the pathogenic relationship between ALS and MG.

Keywords: Amyotrophic lateral sclerosis, myasthenia gravis, coexistence, neuromuscular synapse, retrograde signaling

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is characterized by the degeneration and loss of motor neurons in the cerebral cortex, brainstem, and spinal cord. The mechanisms by which ALS causes motor neuron degeneration remain unclear. Myasthenia gravis (MG) is characterized by weakness and fatigability of muscles. MG is an autoimmune disorder of the neuromuscular junction that is usually caused by antibodies against nicotinic acetylcholine receptors (AChR) and occasionally by antibodies against muscle-specific kinase (MuSK). ALS symptoms can mimic a variety of neurological disorders including MG. However, despite the potential for misdiagnosing ALS and MG, several case reports clearly illustrate that ALS and MG can coexist [1–9]. In this report, we present the case of a patient with clinically probable ALS, who had earlier suffered from MG, which was treated by thymectomy.

CASE REPORT

A 35-year-old Japanese female developed difficulties in speaking, swallowing, and walking, and exhibited ptosis. Because she had been in a psychiatric hospital, her symptoms were overlooked. Twenty-nine years after onset, her symptoms, including muscle weakness in the upper limbs and bulbar palsy, were aggravated. She was then referred to our institution, where she was diagnosed with MG, based on elevated titers of anti-AchR antibodies, a positive edrophonium test, and decremental responses on a repetitive nerve stimulation (RNS) test. Chest CT revealed thymoma; therefore, she underwent thymectomy and was prescribed prednisolone and ambenonium chloride. Subsequently, her symptoms such as dysarthria and muscle weakness disappeared, and only mild

*Correspondence to: Satoshi Yamashita, MD, PhD, Department of Neurology, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan. Tel.: +81 96 373 5893; Fax: +81 96 373 5895; E-mail: y-stsh@kumamoto-u.ac.jp.

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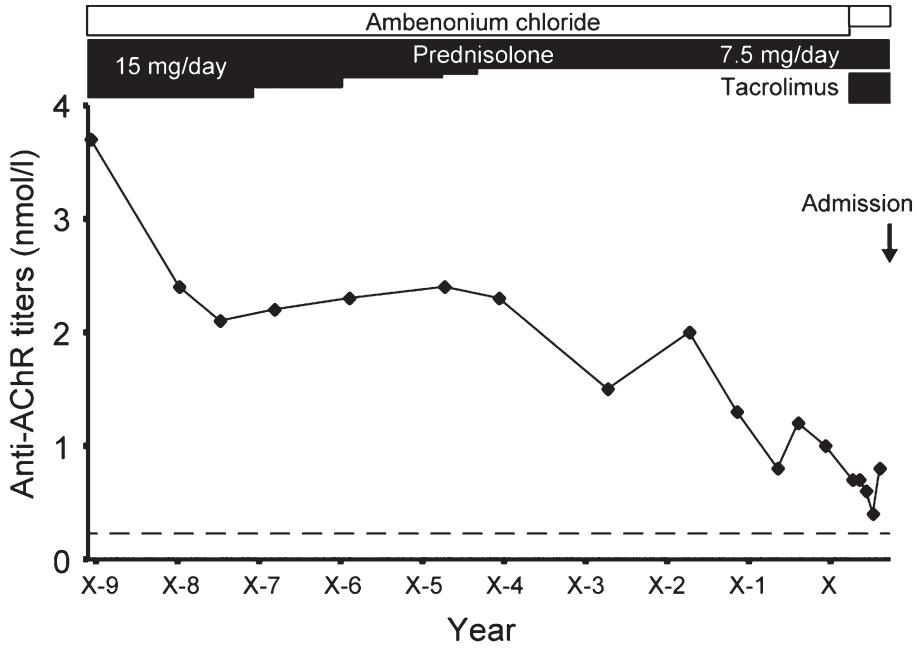

Fig. 1. Variation of anti-acetylcholine receptor (AChR) antibody titers in the patient over time. Horizontal broken line indicates the threshold for detecting anti-AchR antibodies.

ptosis remained. After 12 years, dysphagia and muscle cramping gradually progressed. Chest CT showed no relapse of thymoma. She was prescribed tacrolimus, in addition to prednisolone and ambenonium chloride, but her symptoms persisted. Upon admission to our hospital, neurologic examination revealed that her extraocular muscle movements were normal; however, dysarthria, dysphagia, and tongue atrophy and fasciculation were present, as well as moderate muscle weakness and fasciculation in the upper limbs. Deep tendon reflexes were exaggerated in the lower limbs. Jaw jerk and snout reflex were hyperactive, and Babinski and Chaddock reflexes were present. Titers of anti-AChR antibodies had been elevated during the follow-up periods, but decreased to nearly normal levels after the administration of tacrolimus (Fig. 1). Results of thyroid function tests were normal: TSH 0.80 μIU/ml, free T3 2.29 pg/ml, and free T4 1.12 ng/dl. A pulmonary function test showed decreased forced vital capacity (FVC; 74.4%). Edrophonium tested negative and an RNS test of the facial nerve produced no significant decrement of compound muscle action potentials (CMAP). Cerebrospinal fluid examination revealed no abnormality. Brain MRI showed no abnormalities such as signal hyperintensities of the corticospinal tracts, whereas spinal MRI revealed a slight spondylotic change in the cervical region. Needle electromyography (EMG) revealed widespread giant and polyphasic motor unit potentials, along with fibrillation, positive sharp waves, and fasciculation potentials in the bulbar, cervical, and lumbar regions. She was diagnosed with clinically probable ALS according to the Awaji consensus guidelines [10, 11] and was prescribed riluzole. Her bulbar palsy worsened, and she underwent percutaneous endoscopic gastrostomy. Her respiratory function worsened gradually, and she died due to respiratory failure, 44 years after the onset of MG. Unfortunately, her family members did not consent to an autopsy.

DISCUSSION

We present the case of a patient who developed ALS symptoms, including tongue fasciculation and atrophy, jaw jerk, lower motor neuron signs in the upper limbs (e.g. fasciculations) and upper motor neuron signs in the lower limbs (e.g. Babinski and Chaddock), which gradually developed during follow-up for pre-existing MG. We initially thought that her neurological symptoms might have been aggravated by relapse of MG. However, her test results, which showed that anti-AChR antibody titers were decreasing and that edrophonium was negative, suggested that this was unlikely. Another possibility was that the anticholinesterase inhibitor or the immunosuppressant she

Table 1
Review of cases that report coexistence of myasthenia gravis and amyotrophic lateral sclerosis

Reference	Age	Gender	Initial manifestation	Reflex	Edrophonium test	Needle EMG	RNS	Anti-AchR antibody	Treatment	Thymectomy	Outcome	Duration
Mulder et al. 1959 [1]	49	M	Weakness in the right hand, cramping pain	Hyper	Effective	Acute and chronic denervation	N/A	N/A	N/A	Not done	Worsened	30 mo
	36	F	Weakness in the lower limbs	Hyper	Effective	Acute and chronic denervation	N/A	N/A	N/A	Not done	Worsened	19 mo
	51	M	Weakness in the both arms	Hypo in the upper limbs	Effective	Acute and chronic denervation	N/A	N/A	N/A	Not done	Died	16 mo
	65	M	Atrophy, weaknees and fasciculation in the left shoulder	Hypo in the lower limbs	Effective	Acute and chronic denervation	Waning	N/A	N/A	Not done	Died	10 mo
Ideta et al. 1973 [2]	51	F	Weakness in the right upper limb	Hyper	Partially effective	Chronic denervation	Waxing	N/A	N/A	Not done	N/A	N/A
Sawicka et al. 1985 [3]	52	F	Weakness in the upper limbs	N/A	Effective	Chronic denervation	Waning	N/A	N/A	Done	N/A	60 mo
Noseworthy et al. 1988 [4]	60	F	Ptosis, blurred vision without diplopia, dysarthria, dysphagia, mild weakness of the upper limbs, and weight loss	–	Effective	Acute and chronic denervation	Waning	Negative	Prednisone, pyridostigmine, plasma exchange azat-hioprine	Not done	N/A	N/A
Okuyama et al. 1997 [5]	73	F	Dysphagia	Hyper	Not effective	Acute and chronic denervation	Normal	Positive (0.50 nmol/l)	N/A	Not done	Died	20 mo
Restivo et al. 2000 [6]	53	M	Weakness and atrophy in the right hand, cramping pain	Hyper	Effective	Acute and chronic denervation	Waning	Positive (22.5 nmol/l)	Riluzole, pyridostigmine	Not done	N/A	N/A
Pinto et al. 2008 [7]	71	F	Bilateral ptosis	Hyper	N/A	Acute and chronic denervation	Normal	Negative	Pyrodostigmine	Not done	Worsened	13 mo
	75	F	Bilateral ptosis	Hyper	N/A	Acute and chronic denervation	Normal	Negative	Pyrodostigmine, steroid	Not done	Died	40 mo
Naik et al. 2012 [8]	26	M	Fluctuating diplopia	Hyper	N/A	Acute and chronic denervation	Waning	Positive (8.04 nmol/l)	Pyrodostigmine	Not done	N/A	38 y
Mehanna et al. 2012 [9]	68	F	Severe cramps and weakness in the lower limbs	Hyper in the lower limbs	N/A	Acute and chronic denervation	Normal	Positive (19 nmol/l)	Plasma exchange	Not done	N/A	2 y
Present case	35 (77)	F	Difficulties in speaking, swallowing and ambulation, and blepharoptosis	Hyper	Positive (> negative)	Acute and chronic denervation	Waning (> normal)	Positive (0.80 nmol/l)	Prednisone, a mbenonium, tacrolimus	Done	Died	41 y

N/A, not applicable.

was taking might have impaired her lower motor neurons. However, two observations seem to exclude these possibilities: the reduction of anti-cholinesterase inhibitor did not improve her symptoms, and the onset of muscle weakness and atrophy preceded the administration of tacrolimus. Steroid myopathy was also considered, but the electrophysiological findings were not consistent with steroid myopathy. Furthermore, neither MG relapse, complications related to medications, nor steroid myopathy lead to upper motor neuron signs or to such rapid deterioration. Thus, our patient almost certainly suffered from both MG and ALS.

The prevalences of MG and ALS are 11.8 [12] and 7–11 [13] cases per 100,000 people, respectively. Thus, co-occurrences of MG and ALS are extremely rare. However, despite their rarity, co-occurrences of MG and ALS have been presented in several case reports, suggesting a possible association of the two conditions [1–9]. We summarize these cases in Table 1. The cases can be roughly divided into two groups: one group in which patients diagnosed with ALS subsequently presented clinical symptoms or examination data suggesting myasthenic syndrome [1, 2, 4–7, 9], and a second group in which myasthenic patients subsequently developed ALS symptoms [3, 8]. In the first group, Mulder et al. [1] reported MG in 4 ALS patients based on CMAP decrement on RNS tests. Ideta et al. [2] also found a case of myasthenic syndrome with ALS. Noseworthy et al. [4] reported an unusual case of subacute progressive motor neuronopathy with myasthenia-like features. Okuyama et al. [5] and Mehanna et al. [9] each presented different cases of ALS patients with anti-AChR antibodies. Pinto et al. [7] presented two cases of patients with ALS and ocular ptosis. Restivo et al. [6] showed an unusual association of ALS and myasthenia in a patient treated with riluzole. However, several case studies have shown a significant CMAP decrement on RNS tests and positive edrophonium responses in cases with ALS [14]. Therefore, we should be careful to exclude the apparent coexistence of ALS and myasthenia in this group.

In the latter group, as in the present case, Naik et al. [8] reported the development of ALS in a patient with established seropositive MG, 38 years after the onset. Sawicka et al. [3] showed the case of ALS that developed 3 months after thymectomy in a patient with myasthenia. The coexistence of ALS and MG might be a chance association. However, we postulate that clinicians should not exclude the involvement of motor neuron disease when patients with MG show aggravated symptoms.

A recent linkage study, which analyzed hospital records in the UK, demonstrated that there might be an increased incidence of autoimmune diseases, including MG, before the onset of ALS [15]. As experimental study demonstrated that increasing retrograde signaling by MuSK overexpression stabilized neuromuscular synapses, delayed disease onset, reduced the extent of muscle denervation, and improved motor function in inherited ALS model mice [16]. Although we did not measure the titers of anti-MuSK antibody in this case, the antibodies against the components of neuromuscular junction may interfere with maintenance of neuromuscular synapses, leading to the onset of motor neuron disease. Further investigations will better our understanding of the pathogenic relationship between ALS and MG.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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