Amyotrophic Lateral Sclerosis with Anti-Acetylcholine Receptor Antibody

Yusuke Okuyama, Toshiki Mizuno*, Hideki Inoue** and Kunihiko Kimoto**

We report a case of amyotrophic lateral sclerosis (ALS) with anti-acetylcholine receptor (AChR) antibody in a 73-year-old female patient. She showed the typical course of ALS. She had no clinical findings of myasthenia gravis and had never undergone neurotoxin therapy using snake venom. Anti-AChR antibody was positive with a titer of 0.50 nmol/l on admission. We traced the titers during the progression of ALS; the titer was positive when muscle weakness worsened, and it became negative when the general condition became stable. We suppose that the occurrence of anti-AChR antibody may be partially relevant with abnormalities at the neuromuscular junction during the progression of ALS.

(Internal Medicine 36: 312-315, 1997)

Key words: motor neuron disease, immunological disturbance

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive disorder of upper and lower motor neurons in the cerebral cortex, brain stem, and spinal cord, with clinical manifestation of muscular weakness, atrophy, and hyper-reflexia (1). The onset of this disease is gradual and its clinical course is relentlessly progressive and widespread. However, intelligence and awareness are typically preserved to the end. Although the etiopathogenesis of ALS is still unclear, the possibility of immunological disturbance has been suggested (2). Here, we report a case of ALS with anti-acetylcholine receptor (AChR) antibody which is considered as a specific diagnostic marker for myasthenia gravis (3). We also discuss the significance of the anti-AChR antibody in ALS.

Case Report

A 73-year-old woman was referred to the hospital, complaining of dysphagia in August 1991. She was born of healthy nonconsanguineous parents with no family history of neuromuscular disease. At the time of her birth, the delivery and early development were normal. Physical and psychomotor development had been normal. From November 1990, her voice became husky and the volume had gradually decreased. In March 1991, she developed aphonia and soon dysphagia. In particular, swallowing liquid was more difficult for her than swallowing something solid. She felt no worsening of symptoms when she was tired. On admission, body height was 140 cm and body weight was 37 kg. Her consciousness was alert and the state of nutrition was moderate. Blood pressure was 120/70 mmHg and pulse rate was 76/min and regular. Vision and hearing were not impaired. Neurological examination revealed bulbar palsy. Fasciculation was observed in her tongue and left lower leg. Generalized hyperreflexia and bilateral pathological reflexes were present. No disturbance of the sensory system or autonomic nervous system were observed. Additionally, there was no blepharoptosis at any time. The initial blood count showed a hematocrit of 32.9%, leukocyte count of 4500 with 2% of stab and 62% of segment form, 29% lymphocytes, 6% monocytes. The erythrocyte sedimentation rate was 58 mm/h. Other laboratory data on admission showed normal liver function, serum creatinine 0.8 mg/dl, total protein 7.1 g/dl, albumin 3.9 g/dl. The fraction of serum protein showed albumin 53%, α1-globulin 6.2%, α2-globulin 15.5%, β-globulin 9.5%, and γ-globulin 16.1%. There was no finding of monoclonal gammopathy in the protein-electrophoresis. Serum creatine kinase was 79 IU/l (control range less than 197 IU/l) and there were no abnormalities of electrolytes. Interestingly, serum anti-AChR antibody level was 0.50 nmol/l (control range less than 0.2 nmol/l) and it was positive. The assay of anti-AChR antibody is divided into two types. One measures the activity of

From the Department of Preventive Medicine, Kyoto Prefectural University of Medicine, Kyoto, *the Department of Neurology & Gerontology, Kyoto Prefectural University of Medicine, Kyoto and **the Department of Gastroenterology, Osaka Railway Hospital, Osaka
Received for publication July 11, 1996; Accepted for publication January 28, 1997
Reprint requests should be addressed to Dr. Yusuke Okuyama, the Department of Preventive Medicine, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kamigyo-ku. Kyoto 602
uninhibitory anti-AChR antibody using anti-human IgG, the other measures the activity of inhibitory anti-AChR antibody. In this case, we measured the activity of uninhibitory anti-AChR antibody. Anti-AChR antibody concentration was measured by immunoprecipitation using $^{125}$I-a-bungarotoxin-labeled AChR as the antigen and was expressed as moles of $^{125}$I a-bungarotoxin binding sites precipitated per liter of serum (4).

The initial chest X-ray was normal and thymoma were not found by the chest computed tomography. Tensilon test was negative. The electromyography (EMG) revealed a fasciculation potential in the left-gastrocnemius at rest (Fig. 1), while we could not recognize a fibrillation potential in the EMG. The voltage of neuromuscular units was at the level of 1.5 mV–4.0 mV at voluntary contraction. The interference was poor at maximal contraction. By repetitive stimulation in the left-gastrocnemius, there were no findings of wanning or waxing by the stimulation of left-gastrocnemius with 3 c/s. These findings indicated neurogenic changes. A sagittal scanning of the magnetic resonance image (MRI) showed remarkable tongue atrophy in the anterior half and fatty change of the tongue muscle (Fig. 2). Brain MRI showed no abnormality, except a slight dilatation of the lateral ventricle. Therefore, we made a diagnosis of ALS, not myasthenia gravis. We then started conservative therapy with nasal nutrition. Figure 3 shows the patient's clinical course and the change in serum levels of anti-AChR antibody. We traced the titers of the antibody during the

![Figure 1](image1.png)

**Figure 1. Electromyography in the left-gastrocnemius.** At rest (upper part). At voluntary contraction, a neuromuscular unit which included high voltage with long duration could be recognized (middle part). At maximal contraction, the interference was poor (lower part).

![Figure 2](image2.png)

**Figure 2. Sagittal scanning of tongue MRI.** Remarkable tongue atrophy and fatty change were detected in the anterior half.

![Figure 3](image3.png)

**Figure 3. Clinical course and the change of serum levels of anti-AChR antibody during the progression of ALS.**
In the present case, the patient had never undergone neurotoxin therapy. They had concluded that the positive titer of anti-AChR antibody was 0.50 nmol/l (control range less than 0.25 nmol/l). During the progression of ALS, serum creatinine slightly decreased to a level of 0.4 mg/dl and serum GOT increased to a level of 137 IU/l in April 1992. Although we performed mechanical ventilation, the general condition of the patient gradually worsened and she died of respiratory failure in April 1993. In addition, we could not point out any findings of thymoma, thymic hypertrophy, or other autoimmune disease, such as thyroiditis at autopsy.

**Discussion**

ALS is a neurodegenerative disorder characterized by a progressive loss of motor neurons in the central nervous system. Despite extensive investigation, the etiopathogenesis remains unknown (1). Previous reports showed that a number of factors are associated with the pathogenesis, such as virus infection (5, 6), heavy metal intoxication (7), immunological disturbances (8, 9), metabolic disorders (10), oxidative stress (11), and genetic mutation of the superoxide dismutase gene (12). However, the precise pathogenesis for sporadic cases of ALS remains unclear.

Here, we treated a rare case of ALS with anti-AChR antibody. The immunoassay for anti-AChR antibody is widely used for the diagnosis and the clinical management of patients with myasthenia gravis. Although biological false positive results of this antibody are extremely rare (3), Mittag and Caroscio (13) demonstrated the occurrence of apparent anti-AChR antibody with ALS. The study showed that while the patients with high titers of anti-AChR antibody (1.4–50 nmol/l, control range less than 0.25 nmol/l) had all undergone modified-neurotoxin therapy for ALS, those with low titers (0.39–0.54 nmol/l) had not undergone that therapy. They had concluded that the positivity of anti-AChR antibody was due to a reaction against snake venom, by a neurotoxin therapy (13). On the other hand, Abbott et al (14) demonstrated a female case of ALS with a moderate titer (1.035 nmol/l, control range less than 0.1 nmol/l) of anti-AChR antibody. In that case, the clinical findings of ALS and myasthenia gravis overlapped in the early stage of her illness (14).

In the present case, the patient had never undergone neurotoxin therapy for ALS and had no clinical manifestations for myasthenia gravis. We traced the titers of anti-AChR antibody during the progression of muscle weakness. When muscle weakness of extremities had appeared in August 1991, the titer of anti-AChR antibody was 0.50 nmol/l (control range less than 0.20 nmol/l). In October 1991, about two months after the hospitalization, the titer decreased to the level of 0.20 nmol/l, when the clinical findings were becoming stable. In April 1992, when respiratory muscle weakness developed, the titer slightly increased to 0.25 nmol/l. We could not point out any findings of thymoma, thymic hypertrophy, or other autoimmune disease, such as thyroiditis at autopsy. Therefore, we concluded that this was a rare ALS case with anti-AChR antibody. As far as we know, this is the first report in which the titers of anti-AChR antibody were traced during the progression of ALS.

We suppose that the occurrence of anti-AChR antibody may be partially relevant to the abnormalities at the neuromuscular junction in ALS. Previous reports showed that immunoglobulin (Ig) G from human ALS patients could enhance the release of acetylcholine from axon terminals (15). Human ALS IgG also selectively interacts with calcium channels and alters calcium channel function (16). These phenomena at the neuromuscular junction lead to motor neuron overactivity and may gradually cause muscle weakness. However, the mechanism by which the anti-AChR antibody is produced in ALS is not known. One possibility is that the occurrence of the antibody might be an autoimmune reaction against degenerative AChR at the neuromuscular junction. Further investigation is necessary to define the specific relation with the anti-AChR antibody and the progression of ALS.

**Acknowledgements:** We thank Dr. K. Iwamoto for the analysis of the electromyography. We also thank Dr. K. Marui for his support in the management of the patient.

**References**

11) Bergeron C. Oxidative stress: its role in the pathogenesis of amyotrophic...


