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Postoperative myasthenic crisis successfully treated with immunoadsorption therapy

Junko Ishizeki, Koichi Nishikawa, Fumio Kunimoto, and Fumio Goto

Department of Anesthesiology, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi 371-8511, Japan

Abstract
Myasthenia gravis (MG) is an autoimmune disorder characterized by loss of acetylcholine receptors (AChR) due primarily to the production of anti-AChR autoantibodies. We report a case of MG associated with elevated anti-acetylcholine receptor antibody (anti-AChR Ab) and refractory crisis after thymectomy, in which immunoadsorption therapy was used successfully to stabilize myasthenic symptoms and decrease the anti-AChR Ab titer. A 79-year-old woman underwent extended thymectomy under the diagnosis of MG. One day after surgery she suddenly underwent a myasthenic crisis and was successfully resuscitated. Immunoadsorption therapy with a tryptophan-linked polyvinyl alcohol adsorber was performed three times for the purpose of decreasing the anti-AChR antibodies. The anti-AChR Ab titer was reduced by immunoadsorption during each therapy session; however, the level of anti-AChR Ab before immunoadsorption was higher than that of the previous treatment. This case suggests that the absolute serum level of anti-AChR Ab does not always correlate with the severity of the disease. Removal of pathogenic factors, not only anti-AChR Ab but other antibodies with specificities to skeletal muscles or certain components of the complement system, may contribute to effective treatment of myasthenic crisis.

Key words Immunoadsorption · Myasthenic crisis · Thymectomy

Introduction

Myasthenia gravis (MG) is a disorder of neuromuscular transmission that can be diagnosed by the presence of antibodies to the acetylcholine receptors (AChR); however, some patients with generalized MG do not have detectable AChR antibodies (AChR Ab) [1]. Therefore, the relation of the serum level of anti-AChR Ab and the severity of symptoms is still controversial. In this case report, we describe the time course of changes in the serum anti-AChR Ab titer associated with clinical symptoms.

Address correspondence to: K. Nishikawa
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Case report

A 79-year-old woman, 153 cm in height and weighing 48 kg, had presented with blepharoptosis of both eyelids, dysphagia, diplopia, and muscle weakness of upper limbs for 3 years. Her past history included first degree atrioventricular (AV) block on the electrocardiogram (ECG) and slight hypertension but no severe cardiovascular, respiratory, or neurological complications. She was diagnosed with MG (Osserman's classification IIb—refer to generalized type of MG) based on a positive response to edrophonium and increased titers of antibodies to AChR (7.0 nmol/l; normal < 0.2 nmol/l). Thoracic computed tomography (CT) showed glandular hyperplasia of the thymus. Because her symptoms of generalized muscle weakness, dyspnea, and bulbar paralysis became worse despite anticholinesterase therapy with pyridostigmine bromide (180 mg/day), an extended thymectomy was eventually scheduled. She received pyridostigmine until the morning of the day of surgery. Preoperative examination revealed that the complete blood court, urinalysis, and chemical analysis were normal. She had no history of preoperative myasthenic crisis.

No premedication was given before anesthesia. An 18-gauge peripheral intravenous line in the left forearm and an arterial line in the right radial artery were introduced under local anesthesia. In addition to routine monitors, muscular relaxant monitor, train-of-four (TOF) was used before induction of anesthesia. An epidural catheter was inserted into the T8/9 space for postoperative pain control. Anesthesia was induced with fentanyl (0.1 mg), sodium thiopental (175 mg) and

sevoflurane. A small dose of nondepolarizing muscle relaxant (0.75 mg of vecuronium bromide) was also administered under TOF monitoring to facilitate tracheal intubation. Vecuronium (0.75 mg) and sevoflurane were enough to decrease the TOF ratio to zero, and tracheal intubation was performed at this point. Anesthesia was maintained with 66% nitrous oxide, 33% oxygen, and 1%–2% sevoflurane with continuous infusion of epidural bupivacaine (0.25%, 1 ml/h). Ventilation was adjusted to provide a Pa_{CO_2} of 32–34 mmHg. Because her preoperative blood pressure was high, intravenous administration of nicardipine (total 1.5 mg) was used. No additional muscle relaxants were given during surgery. The duration of surgery was 125 min, and surgical blood loss was 135 ml. After surgery, she was able to start spontaneous breathing in the operating room without using a reversal of the muscle relaxant.

The patient was transferred to the intensive care unit (ICU) with cardiovascular monitoring and remained intubated and spontaneously ventilated for the purpose of respiratory management. The patient's recovery was uneventful. The extubation criteria after thymectomy were clear consciousness, tidal volume of 5 × body weight (kg) ml or more, Pa_{CO_2} of 50 mmHg or less under spontaneous ventilation, Pa_{O_2} of 90 mmHg or more, and respiratory rate of 30/min or less. Because a blood gas analysis revealed that her respiratory state was stable (F_{IO_2} 0.33, pH 7.42, Pa_{O_2} 120 mmHg, Pa_{CO_2} 35.3 mmHg, base excess (BE) –0.9 mEq/l) and she satisfied the criteria, she was extubated and discharged from the ICU on the second postoperative day. However, she complained of severe respiratory discomfort the next morning (pH 7.42, Pa_{O_2} 78 mmHg, Pa_{CO_2} 118 mmHg, BE +8.0 mEq/L) and suffered cardiopulmonary arrest. She returned to the ICU after cardiopulmonary resuscitation. Her serum anti-AChR Ab level was 8.5 nmol/l, which was higher than that measured preoperatively. Blood analysis showed elevated lactate dehydrogenase (LDH) 478 IU/l (normal 119–229 IU/l) and C-reactive protein 9.8; other hepatic and renal function was normal.

Immunoadsorption therapy with a tryptophan-linked polyvinyl alcohol adsorber (IM-TR350; Asahi-Medical, Tokyo, Japan) was carried out every other day, three times in total, to treat the myasthenic crisis. The AChR Ab titer was reduced by immunoadsorption (Fig. 1). Immunoadsorption was performed effectively; in fact, the antibody level was decreased after each treatment. However, the anti-AChR Ab level before immunoadsorption was higher than that of the previous treatment (Fig. 1). With immunoadsorption and steroid therapy (prednisolone 5 mg/day), the patient survived the crisis. Muscle weakness of her upper limbs recovered gradually, and she recovered full consciousness (Glasgow Coma Scale E4V5M6). She scored 2 points

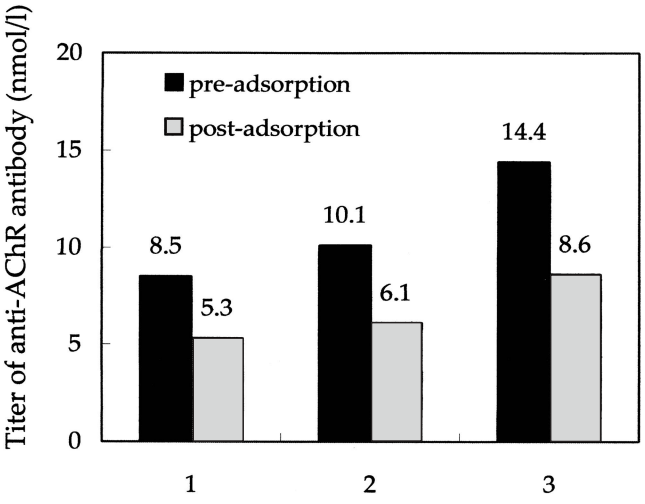

Fig. 1. Serum anti-acetylcholine receptor (*anti-AChR*) antibody was reduced with immunoadsorption therapy. However, each preadsorption titer of anti-AChR Ab increased gradually

(only slight anemia) in the Acute Physiology and Chronic Health Evaluation (APACHE) score. Extubation was performed on day 11 after admission. The following day she was discharged from the ICU, and follow-up was continued on an outpatient basis under steroid treatment.

Discussion

Myasthenia gravis is an autoimmune disease characterized by production of autoantibodies directed against the AChR of the neuromuscular synapse. Previous studies have shown that the disease is antibody-mediated, producing loss of function of skeletal muscle AChRs [2,3]. Three mechanisms have been implicated: (1) autoantibodies against AChR crosslink with AChR and induce endocytosis, resulting in their depletion from the postsynaptic membrane; (2) the autoantibodies directly interfere with AChR function by blocking ACh-binding sites on the receptor; and (3) the autoantibodies contribute to destruction of the endplate with consequent functional receptor loss. The exact mechanism of the MG in our case is unclear, although treatments that try to reduce the level of autoantibodies to AChRs in the serum are reasonable because exacerbation, called myasthenic crisis, involves the respiratory muscle and is life-threatening.

Immunoadsorption therapy using a nonselective tryptophan-linked polyvinyl alcohol adsorber was carried out three times; in fact, the treatments were effective in our case. Immunoadsorption is capable of eliminating huge amounts of immunoglobulin from the patient's circulation with a minimum of the side effects

known to occurs with plasmapheresis. Unfortunately, almost no controlled trials for the application of immunoadsorption have yet been published. Most of the knowledge about immunoadsorption is based on uncontrolled case series and individual observations. A previous case report showed that immunoadsorption therapy was useful for controlling symptoms in patients with severe MG who were otherwise unresponsive [4].

It is generally accepted that the clinical symptoms of MG are correlated with the serum level of anti-AChR antibodies in the individual patient [5]. Despite the well documented role of anti-AChR Ab in MG, the absolute serum level of anti-AChR Ab does not always correlate with the severity of the disease. Each of the preadsorption titers of anti-AChR antibodies was increased gradually, as shown in Fig. 1, even though the clinical symptoms had diminished.

Approximately 80% of MG patients are positive for anti-AChR Ab; the remaining 20% negative for the antibody are referred to as having seronegative MG [6]. Several mechanisms underlying the immunological disorders associated with thymoma have been suggested. The thymoma may trigger abnormal immune responses, resulting in production of various abnormal antibodies such as anti-voltage-gated calcium channel antibody, anti-voltage-gated potassium channel antibody, anti-skeletal muscle antibody, and anti-heart muscle antibody. It has recently been reported that an antibody to muscle-specific kinase (MuSK) is present in approximately 40% of seronegative MG patients [7,8]. Therefore, a possible explanation is that some pathogenic substances such as antibodies to skeletal muscles or certain components of the complement system might have produced postoperative myasthenic crisis. Although we do not know what factors led to her postoperative myasthenic crisis, removal of such antibodies with immunoadsorption therapy may have made her symptoms stabilize.

Preoperatively, in some patients with unstable bulbar symptoms, anti-AChR Ab may be actively produced in thymoma or the adjacent thymus and all peripheral lymph nodes. A thymectomy in such systemic disease may further activate the patient's autoimmunity during the postoperative acute phase. Inoue et al. [9] suggested that adequate preoperative immunosuppressive therapy, such as daily administration of large amounts of corticosteroid, steroid pulse therapy, or plasmapheresis, may contribute to a stable postoperative clinical course in patients with severe bulbar symptoms and a high anti-AChR Ab titer. Watanabe et al. [5] reported prognostic factors for myasthenic crisis after thymectomy in patients with MG. They concluded that postoperative myasthenic crisis was affected by the existence of preoperative bulbar symptoms, a history of preoperative myasthenic crisis, a preoperative serum level of anti-AChR Ab > 100 nmol/l, and intraoperative blood loss > 1000 ml. Our patient satisfied only one of their factors (the existence of preoperative bulbar symptoms). Meticulous preoperative and postoperative care should be carried out to prevent postoperative myasthenic crisis.

Conclusions

We reported a patient with postoperative myasthenic crisis that was successfully treated with immunoadsorption therapy. The anti-AChR Ab titer was reduced through a series of immunoadsorption treatments. It is suggested that removing pathogenic factors—not only anti-AChR Ab but other antibodies with specificities to skeletal muscles or certain components of the complement system—may contribute to effective treatment for myasthenic crisis.

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