

High-dose Intravenous Immunoglobulin for Myasthenia Gravis

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ABSTRACT

An 7-year-old girl with ocular myasthenia gravis (MG) refractory to prednisolone and anticholinesterase compounds was treated with high-dose intravenous immunoglobulin (IVIg). Ocular symptoms disappeared rapidly by the administration of IVIg 300 mg/kg/day for five consecutive days. Booster infusions of IVIg at an interval of 2 weeks appeared to be effective in maintaining a remission at least as an adjunct to prednisolone. The levels of acetylcholine receptor (AChR) antibodies were not correlated with clinical improvement or aggravation. Thus, high-dose IVIg may be useful in refractory cases of MG, allowing a reduction in doses of immunosuppressive drugs.

Key words: *Intravenous immunoglobulin, Myasthenia gravis*

Myasthenia gravis (MG) is a disorder of neuromuscular transmission characterized by fluctuating weakness and fatigability, which is attributed to decreased and altered action of acetylcholine on receptors injured by autoantibodies. Anticholinesterase compounds ameliorate symptoms by slowing hydrolysis of the neurotransmitter, but in patients with more severe disease their efficacy is limited. Though management of MG has been considerably improved by corticosteroids, their limitations include not only their side effects, but also aggravation of MG before improvement and refractoriness of some patients.

High-dose intravenous immunoglobulin (IVIg) has recently been reported to produce improvement in several immunologic disorders, including idiopathic thrombocytopenic purpura (ITP,⁶) autoimmune neutropenia⁸) and antibodies to factor VIII¹⁰). There have been some reports which showed an efficacy of IVIg for generalized MG^{1,3,5}). We treated a patient with ocular MG refractory to several anticholinesterase compounds and prednisolone with IVIg for five consecutive days followed by booster infusions at an interval of 2 weeks.

CASE REPORT

A 2-year-old girl was referred to Hiroshima University Hospital for treatment of ocular MG. She was the product of a normal pregnancy and delivery. She started to have ptosis of the right eye at the age of 1 year and 6 months and consulted

a doctor. Clinical examination and tests confirmed ocular MG without thymoma. She was treated with pyridostigmine and the ocular symptoms improved. However, ocular symptoms gradually worsened, and bilateral ptosis and impaired eye ball movement were observed all day.

Administration of alternate day-prednisolone 20 mg/dose (2 mg/kg) combined with anticholinesterase compounds was initiated at the age of 2 years and 9 months with partial relief. At the age of 3 years and 6 months, ptosis of both eyes and diplopia worsened as the dose of prednisolone was reduced. Prednisolone 20 mg was given on alternate days together with pyridostigmine bromide 90 mg/day and distigmine bromide 5 mg/day and she got some relief from the ocular symptoms. Her ocular symptoms were inversely correlated with the dose of prednisolone and she repeated transient relief and aggravation. She had a prolonged relapse and prednisolone dose was increased to 30 mg on alternate days at the age of 7 years and 4 months without improvement of symptoms. Oral prednisolone 55 mg (2 mg/Kg/dose) was given on alternate days for 4 months, but she failed to make favorable progress. There was no tendency of spontaneous remission during her illness. Because of the unfavorable effects of prednisolone she was treated with high-dose IVIg (Fig. 1).

After informed consent had been obtained, polyethylene glycol-treated intact 7S immunoglobulin (Glovenin I[®], Takeda, Japan) 300 mg/kg/day was

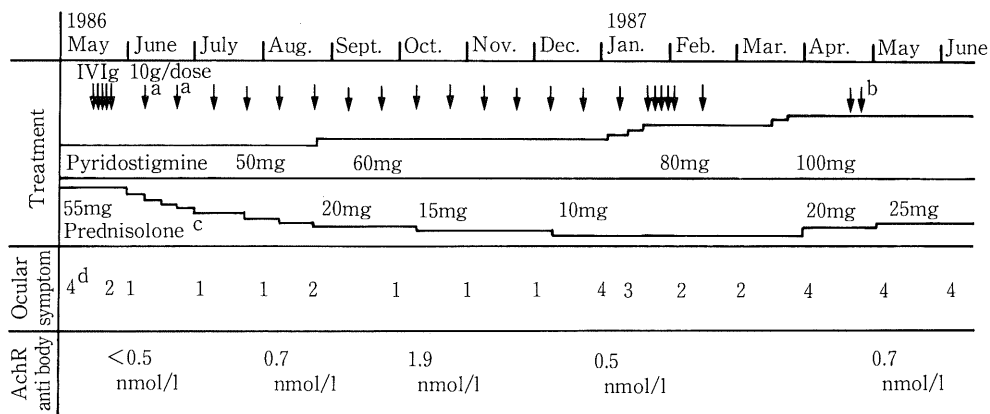


Fig. 1. Chronological summary of the clinical course. Intravenous immunoglobulin (IVIg) 10 g/dose was given except four infusions. Normal range of AchR antibody level is below 0.5 nmol/liter.

Footnotes: a. IVIg 7.5 g/dose was given.

b. IVIg 5 g/dose was given.

c. Prednisolone was given on alternate days.

d. Functional status: 1, asymptomatic; 2, minor symptoms (apparent in the evening); 3, mildly disabled (symptoms readily apparent, with restrictions of more demanding visual activity); 4, severely restricted in the visual activity.

given for five consecutive days at the age of 8 years. The daily dose of anticholinesterase medication was kept constant before and during initial immunoglobulin therapy. Improvement began on day 4 after initiation of IVIg therapy and all the symptoms disappeared within 14 days. This treatment was followed by an observation period of 2 weeks and booster infusion was given every 2 weeks together with oral administration of prednisolone and pyridostigmine. During remission the daily dose of anticholinesterase medication was gradually increased, since it was deemed important to reduce the dose of prednisolone. Ocular symptoms recurred 7 months after initiation of IVIg therapy, when she was receiving pyridostigmine bromide 60 mg/day and prednisolone 10 mg on alternate days. The dose of pyridostigmine was increased, but the improvement of symptoms was unsatisfactory. The booster infusion of immunoglobulin was repeated 5 times every 2 or 3 days. An improvement of the symptoms was noted, but it was not remarkable as that observed at the first five consecutive day-therapy.

At the end of February, 1987, immunoglobulin therapy was discontinued and ocular symptoms gradually worsened. Doses of prednisolone and pyridostigmine were increased, but ocular symptoms did not improve. Because her mother contracted rubella, she received preventive immunoglobulin 5 g/dose. Her ocular symptoms did not improve after this immunoglobulin therapy.

During immunoglobulin therapy, peripheral blood lymphocyte subpopulations were investigated with monoclonal antibodies. A decrease in T4/T8 ratio was occasionally noted, but T4/T8 ratio was not correlated with aggravation or relief of clinical symptoms. As the dose of prednisolone was reduced,

acetylcholine receptor (AchR) antibodies became positive. However, the increase in levels of the antibody titer was not correlated to the aggravation of symptoms.

DISCUSSION

IVIg has recently been reported to improve clinical symptoms of generalized MG^{1,3,5}. We treated a patient with ocular MG with 5-day immunoglobulin therapy followed by boosters every 2 weeks. The rapid improvement was probably related to the high-dose IVIg for 5 days. Especially in children, ocular MG has a variable course with remissions and a high tendency for spontaneous cure. Our patient had a relapse for a long period in spite of a large dose of prednisolone before IVIg and aggravation of symptoms was noted after discontinuation of IVIg. Therefore, it is unlikely that rapid improvement of the symptoms after beginning of IVIg was spontaneous. It is interesting to note the effect of booster infusions. In patients with ITP, a single booster infusion transiently increases platelet count². This indicates that a single booster infusion of immunoglobulin modified immunologic effector process in ITP. The duration of sustained improvement was 6 months in our patient, which was longer than the maximum length of 4 months of another report¹. The improvement of ocular symptoms for a long period in our patient may be, therefore, attributed to the booster infusions of IVIg combined with prednisolone. The effect of the second five-pulsed immunoglobulin therapy in January, 1987, was not dramatic as compared to that of the first pulsed therapy. This indicates that both IVIg and prednisolone dose more than 10 mg on alternate days was needed to bring about complete

relief.

The mechanism of action of IVIg in MG is not known. Although IVIg has been reported to increase T8 cells in patients with MG⁵, it had no demonstrable effect on the total activity of the antibodies *in vivo* and *in vitro*. Arsura et al¹) reported that AchR antibody titer did not change significantly in spite of clinical improvement, although a fall in AchR antibody level was reported in another paper³). In our patient, AchR antibody returned to be positive without aggravation of clinical symptoms. These data indicate that production of AchR antibodies is not suppressed by IVIg *in vivo* and IVIg may inhibit action(s) of antibodies at the neuromuscular junction. Recently, pathogenetic antibodies to determinants at the neuromuscular junction other than AchR have been found in some patients⁷). It is not known whether IVIg has any effect on the production of this type of antibodies.

It has been suggested that anti-idiotypic antibodies may have a regulatory role in MG. Fuchs et al⁴) reported that anti-idiotypic antibodies were successful in suppressing experimental autoimmune MG induced in rabbits by immunization with AchR. Similarly, experimental autoimmune MG passively transferred by a monoclonal AchR antibody could be prevented and reversed by specific anti-idiotypic antibodies¹⁰). However, little is known about the anti-idiotypic antibodies contained in human immunoglobulin preparations.

IVIg has been reported to block the Fc receptor of the reticuloendothelial system in patients with ITP. It is not known how depression in reticuloendothelial function of clearance of circulating immune complexes and excess of monomeric IgG affect deposition of antibody or complement on the postsynaptic membrane of the motor plate.

IVIg therapy results in a prompt and impressive improvement of MG at least as an adjunct to corticosteroids. The relief of the symptoms may be maintained for a long period by booster infusion. High-dose IVIg therapy may be useful in refractory cases of MG, allowing a reduction in doses of immunosuppressive drugs. However, a randomized, double-blind, placebo-controlled study is needed to clarify the true role of IVIg in MG.

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