CASE REPORT

Case of Severe Refractory Myasthenia Gravis in HUKM

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Summary

A 20-year-old girl first noticed bilateral ocular muscle weakness in 2001. Two months later, she developed acute muscle paralysis and respiratory failure which required ventilation. Serum anti-acetylcholine receptor antibodies and repetitive nerve stimulation test was positive and consistent with myasthenia gravis (MG). CT scan thorax revealed thymic enlargement and she underwent a video assisted thymectomy (VATS). However, over the next three years, despite maximal doses of various immunosuppressive agents with plasmapheresis and intravenous immunoglobulin, she was admitted with recurrent myasthenic crisis without any obvious precipitant. She was then commenced on mycophenolate mofetil and together with regular plasmapheresis, cyclosporine and prednisolone, her symptoms have finally improved and brought under control.

Key Words: Myasthenia gravis, Plasmapheresis, Mycophenolate mofetil, Cyclosporine

Introduction

Myasthenia gravis (MG) is an autoimmune neuromuscular junction disorder with significant morbidity and mortality. Conventional treatment with anti-cholinesterases and /or oral steroids usually results in remission. In some cases additional immunosuppressive therapy with either plasma exchange or intravenous immunoglobulin therapy are required. However, a subgroup of patients with generalized MG remain refractory to most conventional treatment modalities leading to recurrent relapses and frequent intensive care unit admissions. These cases of refractory MG are difficult to treat and carry a high mortality. We describe a case of refractory MG with severe and frequent exacerbations who eventually responded to a combination of immunosuppressive treatment regime.

Case Report

A 20-year-old girl first noticed bilateral ocular muscle weakness in 2001 at the age of 16 years. Two months later, she developed acute muscle paralysis and respiratory failure which required ventilation. She was diagnosed with myasthenia gravis and was investigated and treated accordingly. However, the details of her treatment were not available. She had no prior medical problems and was not on any regular medications.

She presented five months later with severe generalized muscle weakness and respiratory failure. She was ventilated for two weeks and was given intravenous immunoglobulin for five days with improvement in muscle power. She had a computed tomography (CT) of the thorax which showed thymic enlargement. Following recovery, she was commenced on pyridostigmine 60mg four- hourly and prednisolone

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15mg thrice daily which was gradually increased. She was then, referred to our hospital for thymectomy.

Examination revealed normal eye movements, bilateral partial ptosis with demonstrable fatigability, moderate nasal and soft speech and a myasthenic 'snarl'. She had bilateral orbicularis oculi and orbicularis oris weakness (grade 3/5), weakness of neck flexion (grade 3/5) and extension (grade 4/5), both upper limbs (grade 4/5) and lower limbs (grade 4 -5/5). Her muscle tone was normal but all her tendon reflexes were increased. She had bilateral Hoffman's sign. Her plantar responses were down-going bilaterally. There was no sensory involvement. Examination of the other systems was unremarkable.

Serum anti–acetylcholine receptor antibodies were present at 0.98nmol/L (normal range -<0.25 nmol/L). Repetitive nerve stimulation test of the right abductor pollicis brevis showed more than 15% decremental response after the 4th stimulus. Other blood investigations which included renal profile, liver profile, full blood count, random blood sugar, thyroid function and creatinine kinase were all normal. Anti-striated muscle antibody and connective tissue screen were negative.

She underwent plasmapheresis three times and had a video assisted thymectomy (VATS). Histopathology revealed a normal thymus and a repeat CT scan thorax showed no residual thymus. She recovered well and was discharged with azathioprine 50mg daily, prednisolone 10mg thrice daily and pyridostigmine 60mg four-hourly.

Two months after her discharge, she suffered another myasthenic crisis secondary to a chest infection. She required ventilation and was given intravenous immunoglobulin for five days with improvement in muscle power. She was discharged with azathioprine now increased to 75mg daily (approximately 2mg/kg/day), prednisolone 40mg daily and pyridostigmine 60mg four-hourly. Despite the above regime, she continued to have recurrent episodes of myasthenic crisis. She was admitted five times in the following ten months with recurrent myasthenic crisis, usually without any obvious precipitant. She was compliant to her therapy.

She initially responded to intravenous immunoglobulin but from the end of 2001, she required plasmapheresis as well. Her symptoms improved after each plasmapharesis. Her prednisolone dose was increased to 60mg daily and pyridostigmine was increased to 120mg four hourly. She was continued on azathioprine 75mg daily but after eight months, the azathioprine was discontinued as she was not showing any improvement. She was started on cyclosporine 100mg twice daily from early 2002 and the dose was increased to 150mg twice daily (5mg/kg/day) after two months. The prednisolone had to be tapered down slowly for fear of steroid induced myopathy.

MRI of the brain, cervical and upper thoracic spine was normal. She showed temporary improvement with cyclosporine and remained well for the next five months and was able to attend school. She then suffered yet another relapse and her cyclosporine was ceased and she was treated with intravenous pulse cyclophosphamide. Despite this, she continued to have recurrent myasthenic crisis and was admitted to hospital almost every 2-3 weeks. Owing to the frequent relapses, she was electively admitted every fortnight for plasmapharesis. In early 2003, she had a repeat VATS to remove any residual thymic tissue. Histopathology revealed thymic hyperplasia. After six monthly pulses of intravenous cyclophosphamide was given with no response, four to six weekly courses of plasmapheresis together with oral mycophenolate mofetil (MMF) 500mg twice daily and cyclosporine were instituted. In 2003 and 2004, she only had one episode of relapse per year when weaning of immunosuppression was attempted.

Currently, she is on oral MMF 500mg twice daily, cyclosporine 75mg twice daily and prednisolone 10mg daily. She continues to require four to six weekly plasmapheresis for symptom control, in addition to pyridostigmine.

Discussion

This is an unusual case of a young patient with MG who has remained refractory to conventional treatment. In view of this 'resistance to treatment' and the presence of Hoffman's sign and hyperreflexia, the possibility of an alternate diagnosis was entertained. However, the neuroimaging studies of the cervical, brain and thoracic spines were normal and thus excluded this possibility. An extended thymectomy to remove any residual thymus also failed to improve her symptoms.

The refractory nature and the recurrent myasthenic crises in this patient had led us to try various combinations of immunosuppressants including pulsed intravenous cyclophosphamide with limited success. This is in contrast to reports by Gladstone *et al*[1] which showed the beneficial effects of high dose cyclophosphamide in a small group of patients with refractory MG. Our current regime which combines the four to six weekly plasmapharesis with mycophenolate mofetil (MMF), cyclosporine and prednisolone have finally ended our desperate attempt to reduce the number of relapses in this patient as each relapse was potentially life-threatening.

MMF is an immunosuppressive agent that inhibits the de novo pathway of guanosine nucleotide synthesis and is well established in transplantation medicine. Its role as an adjunctive therapy in refractory and steroid dependant MG has long been explored.

Meriggiolli and Rowin[2] published their experience in treating a patient with refractory MG with MMF in combination with prednisolone and cyclosporine with significant clinical benefit. Ciafoloni et al[3] demonstrated the beneficial effects of MMF as an adjunctive therapy in an open label pilot study in patients with steroid and/or cyclosporine/azathioprine dependent refractory MG. However, none of the patients described in the study had complementary plasmapharesis or intravenous immunoglobulin with their treatment regimes. This makes our combination of plasmapharesis, MMF, cyclosporin and prednisolone rather unique. To date there has been no trials or case reports on the use of intermittent plasmapharesis in combination with prednisolone, MMF and cyclosporine. Our experience has shown that this combination offers clinical benefit and perhaps should be considered in cases of severe refractory MG cases where other standard therapeutic regimes fail.

In conclusion, this case report illustrates the extreme difficulty in treating cases of severe refractory MG. An aggressive treatment approach using various combinations of immunosuppressants with or without intravenous immunoglobulin/ plasma exchange should be considered in such cases.

References

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