Comparison of Plasmapheresis and Intravenous Immunoglobulin as Maintenance Therapies for Juvenile Myasthenia Gravis

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IMPORTANCE Juvenile myasthenia gravis (MG) is a relatively rare autoimmune disorder. The comparative efficacy of plasmapheresis (PLEX) vs immunoglobulin as maintenance therapy is unclear for this childhood disease.

OBJECTIVE To determine whether PLEX or intravenous immunoglobulin (IVIG) therapy is more effective as maintenance therapy in this disease.

DESIGN, SETTING, AND PARTICIPANTS This retrospective analysis over a 33-year period involved 54 children and adolescents with juvenile MG at a specialized neuromuscular clinic and electromyography laboratory at a tertiary care academic pediatric hospital.

INTERVENTIONS Plasmapheresis and IVIG.

MAIN OUTCOMES AND MEASURES Response to treatment was measured by both improvement in objective physical examination findings and the patients' reported improvement in symptoms and functional abilities.

RESULTS Subjective and objective outcomes correlated well. Both PLEX and IVIG had high response rates. Of the 27 patients with generalized juvenile MG receiving PLEX, IVIG, or both treatments, 7 of 7 patients treated with PLEX alone responded, 5 of 10 patients treated with IVIG alone responded, and 9 of 10 patients who received both responded. There was a significant difference in response rates between patients who received PLEX vs IVIG (P = .04). The youngest age at which PLEX was initiated via peripheral venous access was 9 years, while the youngest child who received IVIG was 9 months old. Thymectomy was performed in 17 children, of whom 11 experienced significant postoperative improvement.

CONCLUSIONS AND RELEVANCE This study provides class III evidence that PLEX and IVIG both have high response rates as maintenance therapies and are reasonable therapeutic options for juvenile MG. Plasmapheresis may have a more consistent response rate than IVIG in this setting. These findings will provide some guidance regarding the approach to therapy for juvenile MG, especially as the results differ somewhat from those of studies focusing on adult MG.
Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction caused by autoantibodies directed against various proteins at the motor end plate, most commonly the acetylcholine receptor (AChR). Juvenile MG arises from autoantibodies that reduce the number of functional AChRs and interfere with normal postsynaptic neuromuscular transmission.

Clinically, MG has 2 major subtypes, primary ocular and generalized. This distinction is valid for both adult and juvenile MG. Although AChR antibodies are measurably elevated in most patients with generalized MG, they are less frequently elevated in ocular MG. Among those who are AChR-antibody negative, IgG autoantibodies to the muscle-specific kinase, striated muscle protein, or low-density lipoprotein receptor–related protein may be elevated.

The goal of treatment for MG is to improve the strength and endurance of a patient by facilitating neuromuscular transmission. This may be accomplished by suppressing the production of abnormal antibodies with medications, such as corticosteroids, or modulating the immune response with intravenous immunoglobulin (IVIG) or plasmapheresis (PLEX). There is a concern regarding the chronic adverse effects of corticosteroid therapy, including weight gain, changes in linear growth, and bone mineralization, that are not entirely reversible. In juvenile MG, immunomodulation with IVIG and PLEX is classically prescribed for sudden exacerbations, preoperative optimization of strength prior to thymectomy, or children who are unable to tolerate or who do not respond to immunosuppressive medications. The benefits of immunomodulation with PLEX and/or IVIG in the situations just mentioned have been demonstrated in several studies, but their comparative effectiveness as maintenance therapies, particularly in juvenile MG, has not been extensively studied.

The aim of our study was to compare the efficacy of PLEX and IVIG for maintenance therapy in patients with juvenile MG. Given the relative paucity of data regarding juvenile MG compared with adult MG, the natural history, diagnostic studies, other medical treatments, and response to thymectomy are also reported.

Methods

Selection of Patients

The Committee on Clinical Investigation (institutional review board) of Boston Children’s Hospital approved this study and issued a waiver of patient consent. The medical records of 54 children and adolescents with a diagnosis of juvenile MG who were seen in the Neuromuscular Program, Electromyography laboratory, or both at Boston Children’s Hospital between 1979 and 2012 were reviewed. The diagnosis of juvenile MG was made based on a combination of patients’ clinical presentation, including onset prior to 18 years, and 1 or more of the following: (1) presence of elevated antibody titers to AChR, muscle-specific kinase, or striated-muscle protein (titin); (2) positive edrophonium test result; (3) a compound motor action potential amplitude decremental response of greater than 10% in response to low-frequency repetitive nerve stimulation; (4) increased jitter on single-fiber electromyography; and/or (5) response to a therapeutic trial. All patients exhibited 1 or more of the following classic hallmarks of MG: fatigable ptosis, ophthalmoplegia, dysarthria (more specifically nasal speech), dysphagia, and extremity weakness. Patients with congenital myasthenic syndrome, neonatal MG, and adult MG were excluded.

Statistical Analysis

Summary statistics were used to evaluate patient characteristics in this sample. For continuous data, summaries consisted of reporting the mean, standard deviation, and minimum and maximum values. For categorical variables, summaries consisted of the number and percentage in each category based on the total sample. A Fisher exact test was used to investigate whether there were significant differences in the responses to IVIG vs PLEX. All reported P values are 2-sided. The statistical analysis was performed using SAS version 9.3.
Classification of Evidence
This retrospective study provides class III evidence that children with juvenile generalized MG have a more consistent response to PLEX than to IVIG therapy.

Results

Demographics
Fifty-four children with juvenile MG were included in the study. Details regarding sex, age at onset, and other aspects of the clinical presentation are listed in Table 1. Seventy percent of our patients had prepubertal onset and 30% had postpubertal onset. There was female predominance in both the pre- and postpubertal age groups. Of note, our youngest patient was a 9-month-old boy with autoimmune ocular MG who had elevated AChR antibodies. Comorbid autoimmune disorders, including rheumatoid arthritis, diabetes mellitus, thyroid disorders, and lupus, were present in 11 of the patients and 19 of their first-degree family members (eTables 1 and 2 in Supplement). One child had juvenile MG as a manifestation of graft vs host disease after a bone marrow transplant for severe combined immunodeficiency and another child had penicillamine-induced MG.

Diagnostic Studies
Acetylcholine-receptor antibodies were assayed in 53 of 54 patients (98%). Antibody testing was performed at Mayo Medical Laboratories, ARUP Laboratories, and/or Athena Diagnostics. One patient with ocular symptoms did not have these antibodies assayed. Elevated AChR antibodies were detected in 35 of 53 cases (66%): 24 of 33 patients (73%) with generalized juvenile MG and in 11 of 20 patients (55%) with ocular myasthenia. In the AChR-antibody seronegative patients, muscle-specific kinase antibodies were independently detected in 3 of 27 (11%) patients and antistriated-muscle antibodies in 3 of 24 patients (13%). Repetitive motor nerve stimulation, edrophonium testing, and stimulated single-fiber electromyography were occasionally used as diagnostic tests to support the diagnosis (Table 1).

Medical Treatment for Ocular Juvenile Myasthenia Gravis
Among the 21 children with ocular juvenile MG, 18 (86%) were initially treated with acetylcholinesterase inhibitors. Seven of the 21 patients (33%) received immunosuppressive therapy with corticosteroids (4 patients), azathioprine (2 patients), or both (1 patient). Five of the 21 (24%) received IVIG and 1 of 21 (5%) received PLEX as monotherapy, while 1 of 21 patients (5%) received both PLEX and IVIG.

Medical Treatment for Generalized Juvenile Myasthenia Gravis
All 33 patients with generalized juvenile MG were treated with acetylcholinesterase inhibitors. Immunosuppressive (corticosteroid or azathioprine) therapy was administered to 13 of 33 patients (39%); 1 of these 13 received both prednisolone and azathioprine. In this group of patients who received immunosuppressive therapy, 5 received IVIG and PLEX; 7 patients re-
received only IVIG. None of our patients received prednisone with PLEX. Twenty-seven of 33 patients (82%) received PLEX and/or IVIG as maintenance therapies. Plasmapheresis was used in 17 of 33 patients (52%) and IVIG was used in 20 of 33 patients (61%). Of these patients, 10 of 33 patients (30%) received both PLEX and IVIG at some point in their course. Six patients had myasthenic crisis with respiratory failure that required intubation and mechanical ventilation. Twelve of 19 children (63%) between the ages of 9 and 18 years with ocular/generalized juvenile MG received PLEX via peripheral access, while 7 of 19 children (37%) between the ages of 6 and 16 years received PLEX via central access.

Outcomes
Follow-up ranged from 0 to 5 years (median, 1 year). Four patients who had single visits or a follow-up period of less than a year were excluded from further analysis. Pharmacologic remission was achieved in 6 of 33 children with generalized juvenile MG and 8 of 21 patients with ocular juvenile MG with anticholinesterase inhibitors alone. Three of 21 patients with ocular juvenile MG had spontaneous resolution of symptoms without any therapeutic intervention. Thirty-seven of 54 patients (69%) required add on of either or combination of immunosuppressive therapy, immunomodulatory therapy with PLEX or IVIG, and thymectomy to achieve remission or improvement in their symptoms. Clinical improvement occurred in 10 of 17 patients (59%) who were taking corticosteroids, 17 of 19 patients (89%) who received PLEX, and 18 of 26 patients (69%) who received IVIG.

Among the children with generalized juvenile MG, the proportion of children who responded to PLEX vs IVIG vs both treatments was significantly different (P = .04, Fisher exact test). For those patients who only received IVIG (n = 10) or PLEX (n = 7), there was also a significant difference in the proportion of patients who responded (50% for IVIG vs 100% for PLEX; P = .04; Fisher exact test). No differences were found when comparing responders between the group receiving both treatments vs IVIG alone (P = .14) and the group receiving both treatments vs PLEX (P > .99) (Table 2).

Among the 21 children with ocular juvenile MG, 7 were treated with IVIG, PLEX, or both. The 1 patient who received both IVIG and PLEX responded, 4 of 5 patients who received IVIG alone responded, and the 1 patient who received PLEX alone responded. These numbers were not large enough to perform a detailed statistical analysis.

Plasmapheresis and IVIG generally had minimal adverse effects and were well tolerated. The 1 significant exception with PLEX was a patient who developed central-line sepsis requiring hospital admission. Two patients developed pyrexia and rigor during the IVIG infusions, necessitating immediate discontinuation of the treatments. These patients were then transitioned to other treatment modalities.

Thymectomy was performed in 16 of 33 patients (52%) with generalized symptoms and 1 of 21 (5%) with ocular symptoms, for a total of 17 patients. This procedure was performed using the sternal approach in 15 patients and via the thorascopic approach in 1 patient. Mean follow-up time was 3.2 years (first quartile, 1 year; third quartile, 6 years).

The myasthenia scale of Millichap and Dodge44–45 was used to grade response to thymectomy as follows: A = complete remission, with medical therapies entirely discontinued; B = good improvement, both objective and subjective, but with continuation of medical therapies at the same or lower dosage; C = slight subjective and/or objective improvement, but significant medical therapies still necessary; D = no change or worse; and E = death of patient. In the 17 children who had received thymectomy, 11 had good response following the surgery, with complete remission (grade A) achieved in 8 and pharmacological remission with pyridostigmine alone (grade B) achieved in 3 others. Of the 11 patients with good responses had early thymectomies. Six remaining children were still receiving IVIG or PLEX at their most recent follow-up visit: 4 of these children were classified as grade C, while 1 was classified as grade D.

The Myasthenia Gravis Foundation of America postintervention status was used as an additional outcome measure for the 17 patients who underwent thymectomy. Among them, 8 patients had complete stable remission with no signs or symptoms for at least 1 year without therapy, 3 patients achieved pharmacologic remission, and 6 patients continued to be symptomatic while taking cholinesterase inhibitors and immunosuppression. Among the patients in the latter group, all had mild symptoms, except for 1 child who continued to be symptomatic requiring a substantial increase in medications. There was no significant difference between the mean follow-up time for patients who had a good response vs those who had a less favorable response.

Pathology reports demonstrated thymoma in 2 of 17 patients, no change in thymic tissue in 1 of 17 patients, lymphoid follicular hyperplasia in 6 of 17 children, and thymic enlargement with increase in B cells and plasma cells in 3 of 17 children. Pathology reports were unavailable for 5 of 17 children.

In Supplement, eFigures 1, 2, and 3 show trends of anti-immunoglobulin.

### Table 2. Patients With Generalized Myasthenia Gravis Who Responded to Each Type of Treatment or Combination of Treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No./No. (%)</th>
<th>Fisher Exact Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IVG Only</td>
<td>Plasmapheresis Only</td>
</tr>
<tr>
<td>All 3 groups</td>
<td>9/10 (90)</td>
<td>5/10 (50)</td>
</tr>
<tr>
<td>IVG vs plasmapheresis**</td>
<td>9/10 (90)</td>
<td>5/10 (50)</td>
</tr>
<tr>
<td>Combination vs plasmapheresis**</td>
<td>9/10 (90)</td>
<td>7/7 (100)</td>
</tr>
<tr>
<td>Combination vs IVIG**</td>
<td>9/10 (90)</td>
<td>5/10 (50)</td>
</tr>
</tbody>
</table>

**Pairwise comparisons.
ies previously suggested that serum antibody titer may be affected by surgical management.\textsuperscript{16,17} In our study population, while a decrease in antibody titer was seen in some children, this was not consistent in all the children or across the different antibody subtypes in the same child. One child in our series, who had a history of thymoma, had a significant increase in antibody titers later in his course, which correlated with a relapse of symptoms. Repeat imaging of the thorax was suspicious for thymoma recurrence.

Discussion

The 3 standard immunomodulatory/immunosuppressive treatments available for MG are corticosteroids, PLEX, and IVIG.\textsuperscript{5,16-20} Long-term corticosteroid therapy is associated with significant adverse effects in children. As a result of the adverse effect profile of corticosteroids, PLEX or IVIG were frequently favored over corticosteroids in our study cohort. Traditionally, PLEX and IVIG are used as immunomodulatory options in acute settings in patients with a myasthenic crisis or those with worsening myasthenic weakness potentially leading to a crisis.\textsuperscript{21-23} Randomized clinical studies carried out in adult populations comparing the efficacies of PLEX and IVIG demonstrate that they are generally comparable, with similar efficacies, durations of benefit, and safety profiles.\textsuperscript{12,24-28}

While the effectiveness of PLEX and IVIG has been established in adult studies, our study is the first attempt to compare the role of PLEX vs IVIG as maintenance therapies for juvenile MG. In our study, we found significant differences in both objective and subjective improvements at follow-up clinic visits in the children with generalized juvenile MG who received PLEX vs IVIG vs combined treatments. There was also a significant difference in the proportion of children who responded when we compared the group who only received IVIG or PLEX. In the children with ocular juvenile myasthenia, our numbers were too small to perform detailed statistical analysis.

The benefits of thymectomy are supported by retrospective adult studies and some pediatric studies.\textsuperscript{29,30} To our knowledge, a prospective, randomized clinical trial of this intervention has not been completed to date in either children or adults. Timing of thymectomy has been controversial in children owing to the incompletely understood role of the thymus in the development of the immune system.\textsuperscript{14} Isolated reports have documented favorable responses to thymectomy in children younger than 6 years of age.\textsuperscript{14,21-31} One series documented a girl with juvenile MG who underwent thymectomy at 17 months of age. She was followed up for 4 years after the surgery, with good improvement and no serious adverse effects.\textsuperscript{14} Current literature recommends thymectomy in affected children and adolescents with generalized myasthenia who are not responding to a treatment regimen of anticholinesterase medications and immunomodulatory or immunosuppressive treatments.\textsuperscript{12,17,24-33}

The strengths of our study included the reasonably large cohort size including the treatment groups for both IVIG and PLEX. The retrospective nature of the study was a limitation, thus the possibility of selection bias for choice of immunomodulatory treatments was not entirely excluded. A more rigorous prospective trial would be difficult given the rare nature of this disease and would most likely require a multicenter cohort. As more studies are published in the future, it will be more feasible to generate more rigorous standards of care.

Conclusions

Cost is a concern when comparing various therapies. Plasmapheresis is more expensive than corticosteroid therapy, and IVIG is extremely expensive. However, corticosteroids carry significant risks of harmful long-term adverse effects that are significantly more consequential in children and adolescents than adults. These include facial changes, weight gain, linear growth deceleration, and bone demineralization. Such adverse effects can have a significant and costly impact on long-term health, thus it is arguable that PLEX and IVIG are cost-effective compared with corticosteroids when long-term outcomes are considered, although precise calculations are beyond the scope of the current study. Our results suggest that PLEX and IVIG both have high response rates as maintenance therapy for juvenile MG, and that both are reasonable alternatives to corticosteroid therapy. Our analysis suggested that PLEX may have a more consistent response rate than IVIG in this setting.
myasthenia gravis. Comparison of IVIg and PLEX in patients with

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of myasthenia gravis with anti-muscle specific

Antibodies and treatments for myasthenia gravis.

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