Combined Immunomodulatory Therapy in Autoimmune Autonomic Ganglionopathy

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Background: Autoimmune autonomic ganglionopathy is a disorder defined by antibodies to the nicotinic acetylcholine receptor of the autonomic ganglia. Patients present with symptoms of autonomic failure, including syncope, orthostatic hypotension, bowel and bladder hypomotility, pupillary dysfunction, and dry mouth and eyes. Symptomatic and immunomodulatory therapy has provided limited clinical benefit in small uncontrolled studies.

Objective: To investigate the effects of combined immunosuppressive therapy and plasmapheresis in autoimmune autonomic ganglionopathy.

Design: Prospective case series.

Setting: Academic medical center.

Patients: Three patients with autoimmune autonomic ganglionopathy who had a limited response to symptomatic therapy, such as midodrine, fludrocortisone, vasopressin, and erythropoietin. Additional treatment with plasmapheresis alone and intravenous immunoglobulin alone provided no additional clinical benefit. Patients underwent 6 months of treatment with prednisone and mycophenolate mofetil followed by 5 cycles of plasma exchange.

Results: Immunosuppressive therapy (prednisone and mycophenolate mofetil) combined with plasmapheresis resulted in substantial improvements in bowel control, pupillary function, dry mouth, and dry eyes. Mean (SD) blood pressure during immunosuppressive therapy was 162/83 (16/12) mm Hg supine and 76/45 (22/11) mm Hg standing (3 minutes). After 5 cycles of plasmapheresis, mean blood pressure was 132/82 (7/4) mm Hg supine and 127/81 (7/1) mm Hg standing (3 minutes; P < .01). Mean antibody level was 7.92 nmol/L on combined immunosuppressive therapy alone and dropped to 0.5 nmol/L after plasmapheresis.

Conclusions: In patients with autoimmune autonomic ganglionopathy, combining immunosuppressive medications prednisone and mycophenolate mofetil with plasmapheresis provides substantial and sustained clinical improvement that was not seen using either treatment alone. Multi-agent immunomodulatory therapies may be necessary to satisfactorily treat this immune-mediated disorder.

Arch Neurol. 2008;65(2):213-217

AUTOIMMUNE AUTONOMIC ganglionopathy is an acquired, immune-mediated disorder that leads to autonomic failure. Patients present with recurrent syncope, orthostatic hypotension, bowel and bladder hypomotility, pupillary dysfunction, and dry mouth and eyes (sicca syndrome). Some cases have rapid onset, while others present with a more indolent course that may mimic a neurodegenerative process. The symptoms of autoimmune autonomic ganglionopathy may be progressive and debilitating and may substantially impair quality of life.

There are no controlled treatment trials for autoimmune autonomic ganglionopathy and only a few case reports of symptomatic therapies for the disease. Some reports suggest that immunomodulatory therapy, such as plasmapheresis or intravenous immunoglobulin (IVIG), may lead to improvement. We describe 3 patients with autoimmune autonomic ganglionopathy who had inadequate responses to symptomatic therapy and exhibited no improvement with plasmapheresis alone, IVIG alone, or immunosuppression using prednisone and mycophenolate mofetil combined. All 3 patients demonstrated substantial clinical and autoimmune neuropathologic improvement when plasmapheresis was repeated following 6 months of maintenance therapy with prednisone and mycophenolate mofetil.
CASE 1

A 49-year-old woman developed syncope, orthostatic hypotension, constipation requiring manual disimpaction, urinary retention requiring self-catheterization, abnormal pupillary light response with blurred vision, and sicca complex (dry eyes and mouth) during several weeks. Nicotinic acetylcholine ganglionic receptor antibody levels were 3100 pmol/L (normal, <50 pmol/L). The patient’s symptoms progressively worsened and led to her transfer to our tertiary care center. Maximal treatment for orthostatic hypotension with 300 mg of L-3,4-dihydroxyphenylserine twice daily, 40 mg of midodrine hydrochloride 4 times daily, 0.4 mg of fludrocortisone acetate once daily, 3000 U of erythropoietin alpha weekly (subcutaneously), and 0.4 mg of vasopressin once daily produced some symptomatic improvement, but frequent syncopal episodes continued and the patient was unable to return to work. Plasmapheresis (5 exchanges) provided no clinical improvement; antibody levels measured 3 days after pheresis were higher than prepheresis levels (3420 pmol/L). Treatment with immunoglobulin (0.4 g of IVIG per kilogram of body weight for 5 days) produced no appreciable benefit. Despite medication adjustments, the patient’s symptoms did not change for 34 months.

CASE 2

A 34-year-old woman presented with rapid onset of syncope, orthostatic hypotension, constipation, urinary retention requiring self-catheterization, abnormal pupillary light response with blurred vision, and sicca complex. Levels of antibodies to the nicotinic acetylcholine receptor (AChR) of the autonomic ganglia were 5900 pmol/L. Symptoms gradually worsened and the patient was transferred for inpatient treatment of orthostatic hypotension. Therapies included 0.4 mg of fludrocortisone acetate daily, 60 mg of pyridostigmine bromide twice daily, 4 mg of vasopressin once daily, 90 mg of pseudoephedrine hydrochloride 4 times daily, and infusions of 2 L of normal saline 3 times weekly. Midodrine hydrochloride was not tolerated owing to severe headache. Plasmapheresis (5 exchanges) and IVIG (0.4 g/kg/d for 5 days) provided no noticeable benefit. On maximal therapy, the patient was unable to stand and was forced to ambulate in a crouched position secondary to orthostatic intolerance. Despite medication adjustments, the patient’s symptoms did not change for 18 months.

CASE 3

A 53-year-old woman presented with gradual onset of orthostatic hypotension, constipation, urinary retention requiring self-catheterization, syncope, abnormal pupillary light response, and sicca complex during 18 months. Levels of antibodies to the nicotinic AChR of the autonomic ganglia were 34 400 pmol/L. Treatment included 30 mg of midodrine hydrochloride 3 times a day, 0.3 mg of fludrocortisone acetate daily, 3000 U of erythropoietin alpha weekly, and 60 mg of pyridostigmine bromide twice daily to improve orthostatic tolerance. Plasmapheresis and IVIG did not provide any measurable improvement. Despite maximal medical therapy, the patient had no substantial change in symptoms for 2 years.

METHODS

PROSPECTIVE THERAPEUTIC PROTOCOL

Treatment involved a combination of prednisone and mycophenolate mofetil for 6 months followed by plasmapheresis:

1. All participants received 1 g of mycophenolate mofetil twice daily.
2. Participants received 60 mg of prednisone daily for 3 months, followed by a gradual dosage taper across 9 months to a minimum dosage of 5 mg every other day.
3. Participants underwent 3 L of plasma exchange (5 exchanges total across 10 days) with 2.5 L of albumin, 5%, and 0.5 L of fresh frozen plasma as replacement. Plasma exchange was performed prior to immunosuppressive therapy and was repeated after 6 months of treatment with prednisone and mycophenolate mofetil.

ANTIBODY DETECTION AND AUTONOMIC TESTING

Antibodies to neuronal ganglionic AChR were detected by radioimmunoprecipitation assay as previously described. Patients underwent autonomic testing at initial diagnosis, the week prior to plasmapheresis (while receiving combined immunosuppressive therapy with prednisone and mycophenolate mofetil), and 1 week postplasmapheresis. Autonomic evaluation included tests of cardiovascular parasympathetic function (heart rate response to the Valsalva maneuver and deep respiration) and cardiovascular sympathetic function (blood pressure response to 45-minute tilt-table testing, 5 minutes of active standing, and the Valsalva maneuver). Patients had continuous electrocardiogram monitoring, continuous beat-to-beat blood pressure recordings, and manual blood pressure measurements every minute during tilt-table testing and active standing for 5 minutes.

RESULTS

Patients reported unequivocal relief from symptoms of orthostatic intolerance immediately after plasmapheresis (while on maintenance immunosuppression). All 3 patients could discontinue medications needed to augment blood pressure and urinate without catheterization for the first time in more than a year. Bowel control improved and dosages of laxative and/or promotility agents were reduced or discontinued. Blurring of vision decreased and pupillary light reflexes were present for the first time since diagnosis.

Antibody levels and autonomic test results at baseline, 1 week prior to plasmapheresis, and 1 week postplasmapheresis are presented in the Table and Figure. The mean changes in sympathetic and parasympathetic function after plasmapheresis were both clinically and statistically significant despite the small number of patients.
We report the use of multi-agent immunosuppressive therapy with plasma exchange as a novel treatment approach in patients with antibody-mediated autoimmune autonomic ganglionopathy who do not respond to symptomatic therapies or single, sequential immunomodulatory therapies alone. Previously reported treatments include volume expansion (fluids, sodium chloride, and fludrocortisone), vasoconstrictors (midodrine hydrochloride, pseudoephedrine, and ephedrine), erythropoietin alpha, pyridostigmine, and nonpharmacologic therapies (compression stockings, abdominal binders, and physical counter maneuvers).\textsuperscript{7,8} Symptomatic therapies produced a modest but incomplete response in our patients. Sequential therapy with plasmapheresis, IVIG, and single-agent immunotherapy also failed to produce an improvement in symptoms. One previously reported patient was treated with the norepinephrine precursor dihydroxyphenylalanine and exhibited a marked clinical response but immunotherapy also failed to produce an improvement.\textsuperscript{6} This evidence suggests that combined therapy for cases resistant to symptomatic therapies may be required to control case reports of plasmapheresis and IVIG use in the treatment of autoimmune autonomic ganglionopathy. A case report of a patient with autoimmune autonomic ganglionopathy provided detailed evidence that plasmapheresis and antibody level reduction improved clinical symptoms and abnormalities on autonomic testing,\textsuperscript{4} while another report documented a therapeutic response to immunoglobulin therapy.\textsuperscript{5} This evidence suggests that combined therapy for autoimmune autonomic ganglionopathy may be required for cases resistant to symptomatic therapies.

**COMMENT**

The AChR of the autonomic ganglia mediates fast synaptic transmission in all peripheral autonomic ganglia and is genetically and immunologically distinct from the AChR at the neuromuscular junction. Antibodies to this receptor, in some series, are present in up to 50% of patients with an idiopathic autonomic neuropathy. Several data suggest that antibodies to the AChR mediate the autonomic features of the disorder: (1) serum ganglionic AChR antibody levels in autoimmune autonomic ganglionopathy correlate with the severity of autonomic neuropathy clinically and on laboratory testing; (2) immunization of rabbits with ganglionic AChR subunit proteins leads to symptoms of autonomic failure similar to those seen in patients with autoimmune autonomic ganglionopathy who have an associated deficit in synaptic transmission in autonomic ganglia; and (3) passive transfer of ganglionic AChR IgG leads to autonomic deficits in mice.\textsuperscript{10}

Patients with autonomic failure due to autoimmune autonomic ganglionopathy exhibit severe orthostatic hypotension, frequent syncope, constipation, nausea, urinary retention, erectile dysfunction, and pupillomotor failure. The symptoms of orthostatic intolerance are usually the most incapacitating manifestation of the disease.

All 3 patients in our study had severe symptoms and high levels of antibodies to the nicotinic AChR of the autonomic ganglia. Treatment with plasmapheresis alone and later with IVIG did not result in clinical improvement or a change in autonomic test results. In case 1, antibody levels that were measured 3 days after 5 cycles of plasmapheresis were higher than antibody levels measured prior to plasmapheresis. Combination immunosuppressive therapy with prednisone and mycophenolate mofetil was insufficient to improve symptoms and autonomic test results until combined with plasma exchange.

These results suggest high and ongoing antibody production. Mycophenolate mofetil reduces antibody-specific T-cell proliferation, the number of B lymphocytes, and therefore the production of autoantibodies. Prednisone causes widespread immunosuppression and also inhibits autoantibody production. Combination treatment with mycophenolate mofetil and prednisone for 6

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**Table. Results of Antibody and Autonomic Testing at Baseline, During Immunosuppression, and After Immunosuppression and Plasmapheresis**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Case 1 Baseline</th>
<th>Case 1 Prepheresis</th>
<th>Case 1 Postpheresis</th>
<th>Case 2 Baseline</th>
<th>Case 2 Prepheresis</th>
<th>Case 2 Postpheresis</th>
<th>Case 3 Baseline</th>
<th>Case 3 Prepheresis</th>
<th>Case 3 Postpheresis</th>
<th>Mean Prepheresis</th>
<th>Mean Postpheresis</th>
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</thead>
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<tr>
<td>Antibody levels, nmol/L</td>
<td>3.10</td>
<td>2.00</td>
<td>0.32</td>
<td>5.90</td>
<td>13.13</td>
<td>1.13</td>
<td>34.40</td>
<td>8.59</td>
<td>0.58</td>
<td>7.92</td>
<td>0.5</td>
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<tr>
<td>Supine BP, mm Hg</td>
<td>156/94</td>
<td>148/96</td>
<td>124/78</td>
<td>164/88</td>
<td>158/74</td>
<td>136/84</td>
<td>168/82</td>
<td>180/78</td>
<td>137/86</td>
<td>162/83</td>
<td>132/83</td>
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<tr>
<td>Standing BP, mm Hg</td>
<td>48/36</td>
<td>62/40</td>
<td>122/81</td>
<td>60/42</td>
<td>65/38</td>
<td>133/80</td>
<td>68/45</td>
<td>103/58</td>
<td>128/82</td>
<td>77/45</td>
<td>128/81</td>
</tr>
<tr>
<td>Fall in standing BP, mm Hg</td>
<td>108/58</td>
<td>86/56</td>
<td>2/−3</td>
<td>104/46</td>
<td>93/36</td>
<td>3/4</td>
<td>100/37</td>
<td>77/20</td>
<td>9/4</td>
<td>85/37</td>
<td>52/4</td>
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<tr>
<td>E/I ratio</td>
<td>1.01</td>
<td>1.01</td>
<td>1.27</td>
<td>1.06</td>
<td>1.10</td>
<td>1.36</td>
<td>1.06</td>
<td>1.08</td>
<td>1.29</td>
<td>1.06</td>
<td>1.31</td>
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<tr>
<td>Valsalva ratio</td>
<td>1.01</td>
<td>1.03</td>
<td>1.32</td>
<td>1.05</td>
<td>1.94</td>
<td>1.18</td>
<td>1.07</td>
<td>1.04</td>
<td>1.22</td>
<td>1.04</td>
<td>1.24</td>
</tr>
<tr>
<td>Fall in tilt BP, mm Hg</td>
<td>98/46</td>
<td>86/44</td>
<td>4/1</td>
<td>106/52</td>
<td>94/44</td>
<td>4/4</td>
<td>112/47</td>
<td>111/33</td>
<td>6/5</td>
<td>97/46</td>
<td>52/4</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; E/I ratio, expiration to inspiration ratio.

\*Patient on treatment with prednisone and mycophenolate mofetil, 1 week before plasmapheresis.

\+Patient on treatment with prednisone and mycophenolate mofetil, 1 week after plasmapheresis.

\^P<.05.

\(\text{Fall in standing BP, mm Hg}\)\text{P}<.01, compared with mean prepheresis values.

\(\text{Ratio of maximal to minimal heart rate during a Valsalva maneuver.}\)
months did not reduce antibody production to levels adequate for clinical benefit in our patients. Only after the addition of plasma exchange, leading to direct antibody removal, was there evidence of improvement in autonomic function. One of the previously reported cases, initially responsive to plasma exchange, required therapy with prednisone and azathioprine following a second relapse.5

Treatments for autoimmune autonomic ganglionopathy have been primarily symptomatic, and reports of immune modulation are limited to small, uncontrolled case studies. Our current study, though small, demonstrates a substantial clinical response with combined immunomodulatory therapy in patients in whom all prior immune-modulating therapies failed. Further study is needed—ideally, controlled multicenter trials—given the small number of patients with this disorder. However, these preliminary results suggest that combined immunosuppressive therapy in conjunction with plasmapheresis may be necessary to provide therapeutic benefit in refractory cases of this disabling disease.

**Figure.** Autonomic testing results in case 1 prior to therapy (A and B), during maximal symptomatic treatment (C and D), and after combination therapy with prednisone, mycophenolate mofetil, and plasmapheresis (E and F). Valsalva maneuver results are shown (A, C, and E); note the progressive improvement in phase 2 recovery, blood pressure overshoot, and increase in heart rate variability during maximal therapy (E). Tilt-table test results are shown (B, D, and F); note the dramatic falls in blood pressure prior to therapy and even on maximal symptomatic treatment (B and D) that resolve after combination therapy with prednisone, mycophenolate mofetil, and plasmapheresis.
Accepted for Publication: September 25, 2007.
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REFERENCES


Announcement

Trial Registration Required. In concert with the International Committee of Medical Journal Editors (ICMJE), Archives of Neurology will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment before this date, registration will be required by September 13, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorial by DeAngelis et al in the January issue of Archives of Dermatology (2005;141:76-77). Also see the Instructions to Authors on our Web site: www.archneurol.com.