Autologous Hematopoietic Stem Cell Transplantation (auto-HSCT) has been used successfully to treat patients with autoimmune diseases such as multiple sclerosis and scleroderma that are resistant to more conventional therapy. A conditioning regimen of high-dose chemotherapy and antilymphocyte antibodies eliminates diseased immune cells. A naive immune system is subsequently regenerated from an infusion of autologous hematopoietic stem cells (auto-HSCs). Patients with other rare, severe autoimmune neurological diseases may benefit from auto-HSCT.

Stiff Person Syndrome

Stiff person syndrome (SPS) is a rare neurological disease causing significant functional disability for patients and presenting a therapeutic challenge for clinicians. The resolution of clinical manifestations of SPS despite the persistence of anti-glutamic acid decarboxylase antibodies following auto-HSCT suggests that the antibody does not play a direct role in pathogenesis of SPS.

Report of Cases

Case 1
A woman was diagnosed in August 2005 as having SPS at age 48 years after presenting with progressive leg stiffness, hyperreflexia, and falls. Her reflexes were brisk but she had normal muscle tone and strength. She walked with an abnormal gait. She was treated with benzodiazepines, but her symptoms worsened. Treatment with oral immunomodulating agents including intravenous immunoglobulin, plasma exchange, and rituximab has been used to control disease activity.

Based on prior experience using auto-HSCT for autoimmune diseases, the Ottawa Hospital Blood and Marrow Transplant Program performed auto-HSCT on 2 patients with severe SPS based on a regimen used for patients with multiple sclerosis. Assembly and publication of these cases were approved by the Ottawa Hospital Research Institute Research Ethics Board. The research ethics board approved the retrospective collection, analysis, and publication of data from the medical records. Informed consent from the patients was not requested by the research ethics board.

Two anti–glutamic acid decarboxylase antibody–positive patients with SPS had an autologous hematopoietic stem cell graft collected and stored. Subsequently, the patients underwent auto-HSCT. Both patients achieved clinical remission with sustained, marked improvement in symptoms and a return to premorbid functioning, now more than 2.5 and 4.5 years after the procedure.

CONCLUSIONS AND RELEVANCE
Stiff person syndrome represents a novel indication for auto-HSCT. The resolution of clinical manifestations of SPS despite the persistence of anti-glutamic acid decarboxylase antibodies following auto-HSCT suggests that the antibody does not play a direct role in pathogenesis of SPS.

IMPORTANCE
Stiff person syndrome (SPS) is a rare neurological disease causing significant functional disability for patients and presenting a therapeutic challenge for clinicians. Autologous hematopoietic stem cell transplantation (auto-HSCT) has been used successfully to remit autoimmune-mediated neurological diseases. We report 2 cases of severe SPS treated with auto-HSCT, a novel therapy for this disease.

OBSERVATIONS
Two anti–glutamic acid decarboxylase antibody–positive patients with SPS had an autologous hematopoietic stem cell graft collected and stored. Subsequently, the patients underwent auto-HSCT. Both patients achieved clinical remission with sustained, marked improvement in symptoms and a return to premorbid functioning, now more than 2.5 and 4.5 years after the procedure.

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Stem Cell Transplant for Stiff Person Syndrome

Case Report/Case Series

Research

“tin solider” gait. Findings on magnetic resonance imaging of her brain and spine as well as electromyograms were normal. Anti-GAD antibodies were present at a very high titer of 127 U/mL.

The patient’s symptoms worsened during the next 3 years. She developed episodic spasms triggered by loud sounds and cold temperatures. She began treatment with diazepam, baclofen, tinzamide hydrochloride, and vigabatrin. Immunomodulation with intravenous immunoglobulin, azathioprine, and monthly plasma exchange provided only temporary relief. By November 2008, she needed 45 minutes each morning to allow the diazepam to begin working before she was able to get out of bed. She was having frequent falls resulting in minor trauma despite using mobility aids. She was no longer able to work and became socially withdrawn because of the functional limitations and reluctance to leave home.

In April 2009, an auto-HSC graft was mobilized with cyclophosphamide, 2.5 g/m², intravenously followed by granulocyte colony-stimulating factor, 10 μg/kg, subcutaneously daily for 9 days in April 2009. CD34+ selection of the graft was performed to deplete the graft product of immune cells prior to its cryopreservation. In May 2009, the patient underwent immunoablation with busulfan, cyclophosphamide, and rabbit antithymocyte globulin (Figure) followed by reinfusion of stem cells. Details about the auto-HSCT are summarized in the Table.

One month following transplantation, the symptoms related to SPS had resolved. The patient no longer experienced episodic spasms. Two months after transplantation, the anti-GAD antibody titer was 87 U/mL. Diazepam and antispasmodic agents were weaned slowly during a 3-year period and were fully discontinued by May 2012. She was fully mobile without the need for mobility aids 6 months after transplantation. She returned to work and full premorbid functioning, including being able to pursue sports such as skiing and bicycling. She remains asymptomatic 4 years 8 months following transplantation.

Case 2

An otherwise healthy woman had episodic leg muscle stiffening lasting several hours. Episodes were triggered by cold weather or stress 3 or 4 times per week starting in 2006. Findings on neurological examination between attacks were entirely normal. Electromyography demonstrated continuous motor unit activity, and there was a low titer of anti-GAD antibody (5.6 U/mL), ultimately leading to a diagnosis of SPS in 2008 at age 30 years.

During the next 2 years, she was treated with daily baclofen and diazepam. Immunomodulation included biweekly intravenous immunoglobulin and plasma exchange. However, the spasms became more severe and affected the upper limbs and respiratory muscles, resulting in suffocation-like dyspnea. She required midazolam hydrochloride and propofol for symptom relief. In the year prior to auto-HSCT, she made 47 emergency medical services calls with subsequent hospital visits and had required an intensive care unit admission (but not mechanical ventilation) as well as a hospital admission for more than 3 months. She was frightened to be alone as it became impossible to call for assistance once an attack began. She stopped working and driving and had moved back into her parents’ home.

In April 2011, an auto-HSC graft was mobilized with cyclophosphamide, 2.5 g/m², intravenously followed by granulocyte colony-stimulating factor, 10 μg/kg, subcutaneously daily for 9 days. She did not experience complications during this process. In May 2011, she underwent immunoablation with busulfan, cyclophosphamide, and rabbit antithymocyte globulin followed by reinfusion of the CD34+ selected auto-HSCT graft (Figure). Details about the auto-HSCT are summarized in the Table.

The patient had 2 episodes of severe muscle spasms requiring emergent treatment in the first 2.5 months after auto-HSCT. A third episode occurred within 6 months of transplantation and was prompted by a serious motor vehicle crash occurring in her proximity. A fourth episode occurred 18 months following transplantation. The latter 2 episodes were less severe, were of shorter duration, and resolved without medication. They did not require attention from emergency medical services. She has been able to return to work and full premorbid activity. She has not had symptoms related to SPS in longer than a year and is slowly tapering her use of baclofen and diazepam.

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### Figure. Immunoablative Regimens

A

- Busulfan, 2.4 mg/kg/d
- Cyclophosphamide, 60 mg/kg/d
- Rabbit antithymocyte globulin, 1.25 mg/kg/d

CD34+-selected auto-HSCT

Pretransplant Time, d

B

- Busulfan, 2.4 mg/kg/d
- Cyclophosphamide, 50 mg/kg/d
- Rabbit antithymocyte globulin, 1.25 mg/kg/d

CD34+-selected auto-HSCT

Pretransplant Time, d

Immunosuppressive regimens for case 1 (A) and case 2 (B). Auto-HSCT indicates autologous hematopoietic stem cell transplantation.

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We describe 2 patients with severe SPS who are in clinical remission after intensive immunoablation followed by auto-HSCT. Both patients remain in remission without ongoing immunomodulatory or immunosuppressant medication, and both have returned to their normal premorbid functioning. To our knowledge, this is the first report documenting that immunoablation followed by auto-HSCT can produce long-lasting and complete remission of SPS. Neither patient experienced unexpected treatment-related toxic effects. Intriguingly, about 10% of patients undergoing auto-HSCT for autoimmune diseases have developed secondary autoimmune phenomena, including a single case of SPS. While these patients did not experience unexpected toxic effects, one must be cognizant of possible neuromuscular drug-related toxic effects in this vulnerable patient group.

Both patients received a rigorous immunoablative regimen to eliminate the destructive autoimmunity responsible for SPS. This was followed by infusion of an auto-HSC graft depleted of residual immune cells that allowed the reestablishment of a naive self-tolerant immune system. While less intense conditioning may result in lower treatment-related morbidity, this high-dose approach may be required to minimize the likelihood of relapse as has been seen when less intense approaches have been used for other autoimmune diseases. The risks of auto-HSCT can be minimized when patients are managed in expert units with current standards of supportive care, including chemoprophylaxis against infection and monitoring for opportunistic infectious agents.

The changes in the immune system following auto-HSCT have been well documented for patients with other autoimmune diseases. The rapid improvement in both patients after auto-HSCT suggests that immune-mediated mechanisms are responsible for the symptoms associated with SPS. The exact mechanism by which the immune system causes changes in neuromuscular function is uncertain. While anti-GAD antibodies may serve as a biomarker of the illness, it is unlikely that they are involved in the pathogenesis of disease activity. Clinical activity resolved in case 1 even with continued circulating anti-GAD antibodies, similar to a previously described patient treated with rituximab.

Intense immunoablation and CD34+ selected auto-HSCT resulted in disease resolution in 2 patients with severe SPS. The evidence supporting auto-HSCT as treatment for autoimmune neurological diseases other than multiple sclerosis is limited to anecdotes and small case series. Patients with rare conditions undergoing developmental transplantation should be reported to one of the international transplant registries (the Center for International Blood and Marrow Transplant Research or the European Group for Blood and Marrow Transplantation) to facilitate comparisons of different approaches, monitoring of late effects, and dissemination of individual centers’ experiences to the larger medical community.

### Table. Patient, Graft, and Transplantation Information

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at auto-HSCT, y</td>
<td>53</td>
<td>33</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Year of auto-HSCT</td>
<td>2009</td>
<td>2011</td>
</tr>
<tr>
<td><strong>Collection outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graft composition, cells/kg&lt;sup&gt;CD34⁺&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before selection</td>
<td>14.84 × 10⁶</td>
<td>26.87 × 10⁶</td>
</tr>
<tr>
<td>After selection</td>
<td>4.6 × 10⁶</td>
<td>8.6 × 10⁶</td>
</tr>
<tr>
<td>Graft composition, cells/kg&lt;sup&gt;CD3⁷⁺&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before selection</td>
<td>33.53 × 10⁶</td>
<td>92.86 × 10⁶</td>
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<tr>
<td>After selection</td>
<td>2.04 × 10⁶</td>
<td>0.07 × 10⁶</td>
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<tr>
<td><strong>Transplant outcome</strong></td>
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<td></td>
</tr>
<tr>
<td>Length of hospital stay, d</td>
<td>32</td>
<td>41</td>
</tr>
<tr>
<td>Time to absolute neutrophil count &gt;500/μL, d</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Time to platelet count &gt;20 × 10⁹/μL, d</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Packed red blood cell units transfused, No.</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Single-donor apheresis platelet units transfused, No.</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Acute regimen-related toxic effects&lt;sup&gt;⁸&lt;/sup&gt;</td>
<td>Pancytopenia</td>
<td>Pancytopenia</td>
</tr>
<tr>
<td>Infectious complications&lt;sup&gt;⁹&lt;/sup&gt;</td>
<td>Herpes simplex virus-related rash</td>
<td>None</td>
</tr>
<tr>
<td><strong>Status and length of follow-up, mo</strong></td>
<td>Alive, 56 mo</td>
<td>Alive, 32 mo</td>
</tr>
</tbody>
</table>

**Abbreviation:** Auto-HSCT, autologous hematopoietic stem cell transplantation.

**SI conversion factors:** To convert neutrophils to ×10⁹ per liter, multiply by 0.001; to convert platelets to ×10¹² per liter, multiply by 1.0.

<sup>⁴</sup> Miltenyi CliniMACS CD34⁺ selection system used for graft processing.

<sup>⁸</sup> From 11 days before auto-HSCT to 30 days after auto-HSCT.


