ARTICLE CLASS OF EVIDENCE

Autologous Hematopoietic Stem Cell Transplantation for Stiff-Person Spectrum Disorder

A Clinical Trial

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Abstract

Objective

To test the hypothesis that autologous nonmyeloablative hematopoietic stem cell transplantation (HSCT) is safe and shows efficacy in the treatment of stiff-person spectrum disorder (SPSD).

Methods

Twenty-three participants were treated in a prospective open-label cohort study of safety and efficacy. After stem cell mobilization with cyclophosphamide (2 g/m^2) and filgrastim (5–10 μg/kg/d), participants were treated with cyclophosphamide (200 mg/kg) divided as 50 mg/kg IV on day −5 to day −2; rabbit anti-thymocyte globulin (thymoglobulin) given intravenously at 0.5 mg/kg on day −5, 1 mg/kg on days −4 and −3, and 1.5 mg/kg on days −2, and −1 (total dose 5.5 mg/kg); and rituximab 500 mg IV on days −6 and +1. Unselected peripheral blood stem cells were infused on day 0. Safety was assessed by survival and National Cancer Institute common toxicity criteria for adverse events during HSCT. Outcome was assessed by ≥50% decrease or discontinuation of antispasmodic drugs and by quality of life instruments.

Results

There was no treatment-related mortality. One participant died 1 year after transplantation of disease progression. Of the 74% of participants who responded, 47% have stayed in remission for a mean of 3.5 years; 26% did not respond. Compared to nonresponders, responders were more likely to have pretransplantation intermittent muscle spasms (16 of 17 vs 0 of 6), normal reflexes (12 of 17 vs 0 of 6), and positive CSF anti–glutamic acid decarboxylase serology (12 of 14 vs 2 of 6). Compared to responders, nonresponders were more likely to have lead pipe rigidity (4 of 6 vs 0 of 17) and EMG-documented simultaneous contraction of agonist/antagonist limb muscles (4 of 6 vs 1 of 17). Pre-HSCT use of prescription serotonin selective receptor inhibitor (SSRI) or serotonin and norepinephrine reuptake inhibitor (SNRI) was more common in those who relapsed or never responded (9 of 12) compared to those responders who never relapsed (0 of 11).

Conclusion

In this cohort, HSCT was safe, but the beneficial effect of HSCT was variable and confined predominately to participants with episodic spasms and normal tendon reflexes without simultaneous cocontraction of limb agonist/antagonist muscles who were not taking SSRI or SNRI antidepressants.

Classification of Evidence

This study provides Class IV evidence that, for a subset of people with SPSD, autologous nonmyeloablative HSCT improves outcomes.

ClinicalTrials.gov Identifier

NCT02282514.

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Glossary

CI = confidence interval; **CPAQ** = Chronic Pain Acceptance Questionnaire; **GAD** = glutamic acid decarboxylase; **HSC** = hematopoietic stem cell; **HSCT** = HSC transplantation; **IVIG** = IV immunoglobulin; **MS** = multiple sclerosis; **MSC** = mesenchymal stem cell; **NSC** = neural stem cell; **PERM** = progressive encephalomyelitis with rigidity and clonus; **SF-36** = Short Form 36; **SNRI** = serotonin and norepinephrine reuptake inhibitor; **SSRI** = serotonin selective receptor inhibitor; **SPS** = stiff-person syndrome; **SPSD** = stiff-person spectrum disorder.

Stiff-person spectrum disorder (SPSD) is a rare neurologic disorder (affects 1 in 1 million people) causing persistent stiffness and rigidity.[1,2] Periodic painful muscle spasms vary in frequency, becoming continuous in severe cases, and are often induced by heightened startle responses to noise, touch, or anxiety. Phobias about leaving the house develop due to risk of falls from paraspinal muscle spasms that may become severe enough to cause joint subluxation, bone fractures, recurrent hospitalization, use of IV analgesia, or placement of an intrathecal baclofen pump.[1–3] Reflexes may be normal or increased with or without clonus.[4] Involuntary steady resistance to examiner-attempted limb movement, that is, lead pipe rigidity, may be present at ≥1 joints. Participants may require the use of a cane, walker, or wheelchair or in severe cases may become bedridden.[1,2]

SPSD may also be accompanied by seizures, cerebellar ataxia, respiratory arrest from pharyngeal, chest wall, diaphragmatic spasms, or autonomic dysfunction with labile blood pressure, cardiac dysrhythmias, abdominal pain, nausea, vomiting, regurgitation, or diarrhea.[5] Other autoimmune diseases such as thyroiditis, type I diabetes mellitus, vitiligo, and celiac disease may accompany SPSD.[6]

SPSD is thought to arise from immune-mediated loss of GABA-inhibitory neurotransmission resulting in unchecked and persistent neurostimulation.[7] It is usually, but not always, associated with various autoantibodies that impair production, transport, or release of the inhibitory neurotransmitter GABA. The most common autoantibody associated with SPSD is directed toward glutamic acid decarboxylase (anti-GAD).[8–10] A variety of other antibodies may be associated with SPSD, including antibodies to the glycine receptor, gephyrin, amphiphysin, or dipeptidyl peptidase-like protein 6.[10] Glycine receptor antibodies are associated with a unique SPSD presentation that manifests as progressive encephalomyelitis with rigidity and clonus (PERM)[10] but are also present in ≈15% of participants with typical stiff-person syndrome (SPS).[11] Antibodies to amphiphysin are associated with the paraneoplastic variant of SPSD.[12,13] While the pathophysiology is thought to be immune-mediated, despite current immune therapies, the clinical course is progressive, and autopsy of individuals in the later stages of disease may demonstrate neuronal loss, which raises the possibility of a late neurodegenerative phase.[14–16]

Stiffness and spasms are treated symptomatically with benzodiazepines and muscle relaxants such as baclofen.[1,2] Immunotherapy options include corticosteroids, plasmapheresis, IV immunoglobulin (IVIG), and rituximab.[1,2] IVIG has reduced stiffness in a randomized controlled trial,[17] while rituximab, although commonly used,[18–20] failed in a randomized trial compared to placebo.[21]

SPSD is a clinical diagnosis based on axial muscle stiffness; superimposed painful muscle spasms induced by anxiety, tactile, or auditory stimuli; electrophysiologic evidence of continuous motor unit activity; positive anti-GAD antibodies; and response to diazepam.[1,2,22] There is, however, no specific test that confirms the diagnosis.[23] Anti-GAD antibodies are not mandatory for diagnosis and may be positive or absent from the peripheral blood, CSF, or both.[10] Similarly, continuous motor unit activity may be intermittent, may be inhibited by antispasmodic medications, may occur by intentional volition, or may be found in normal individuals who are unable to relax their paraspinal muscles.[24] There are no formal criteria defining different disease stages, that is, early immune-mediated vs late degenerative phase, and there is no universally agreed-on definition of a treatment response.

In 2000, it was suggested that a diagnosis of SPS should be based on the presence of rigidity and spasms in both the trunk and limb muscles in the presence of cocontraction of agonist and antagonist muscles.[25] In 2016, Martinez-Hernandez et al.[10] suggested the term SPSD as a spectrum of clinical and antibody presentations that may involve rigidity and spasms in trunk muscles only.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Northwestern University Institutional Review Board and listed in ClinicalTrials.gov (identifier: NCT02282514). Anti-GAD antibodies were performed by a commercial laboratory (Quest diagnostics) with an ELISA assay.

Eligibility

When the study was registered in 2014, we were initially planning to enroll 10 participants. However, after the first participant did extremely well, and as the study progressed, we were inundated with referrals and increased enrollment up to 40 participants. After we treated several more (23) participants, some were not responding, and others were relapsing. Because it was unclear from the data available and from the pretransplantation

evaluation how to identify which participants would respond or not respond to hematopoietic stem cell transplantation (HSCT), further enrollment was terminated. We stopped enrollment to protect future patients who would have no beneficial effect from the risks of exposure to high-dose chemotherapy and in order to follow up the participants who had already been treated in the hope of obtaining a better understanding of the factors that underpin the response to autologous HSCT.

Criteria for enrollment were age between 18 and 60 years, a clinical diagnosis of SPSD with axial muscle stiffness, painful muscle spasms, EMG confirmation of continuous paraspinal muscle activity, or simultaneous cocontraction in opposing limb agonist/antagonist muscles and anti-GAD antibody in the peripheral blood or CSF. Participants must have tried and be dependent on or intolerant of a benzodiazepine and IVIG. All participants had peripheral blood draws for anti-GAD and anti-amphiphysin antibodies, but not for dipeptidyl peptidase-like protein 6 or glycine receptor antibodies. A lumbar puncture was performed for cerebrospinal anti-GAD antibody.

Exclusion criteria were history of cancer or seropositive for amphiphysin antibody; an MRI of the cervical, thoracic, and lumbar sacral spine that identified another possible confounding etiology (i.e., nerve root compression, ankylosing spondylitis, multiple sclerosis [MS]); cardiac left ventricular ejection fraction <55%; pulmonary D_{LCO} <60%; renal creatinine >2.0 mg/dL; liver transaminases >2 times the upper limit of normal; platelet count <100,000/μL; or HIV or hepatitis B or C seropositivity.

Stem Cell Harvest and Conditioning Regimen

Peripheral blood stem cells were collected 10 days after IV cyclophosphamide (2 g/m^2) and 5 to 10 μg/kg/d of subcutaneous filgrastim beginning 5 days after cyclophosphamide. The immune ablative regimen was intravenous cyclophosphamide 50 mg/kg/d on days −5 to −2 before stem cell infusion (day 0); rabbit anti-thymocyte globulin 0.5 mg/kg on day −5, 1.0 mg/kg on days −4 and −3, and 1.5 mg/kg on days −2 and −1; and rituximab 500 mg on days −6 and +1.

In-participant transplant grade 3 and 4 toxicities were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 2.0). Broad-spectrum IV cefepime or piperacillin/tazobactam was started when neutropenic, and oral ciprofloxacin and isavuconazonium were started on day +2 and continued until absolute neutrophil count rose to >500/μl. Fluconazole (400 mg orally daily) was started on discharge and continued for 3 months. Acyclovir (400 mg orally twice daily) was started on admission and continued for 1 year. Bactrim (1 oral double strength 3 times a week) was started when the platelet count rose to >100,000/μL and continued for 3 months. Participants were contacted to return at 6 months and then yearly.

Outcome

The primary end point was safety and National Cancer Institute common toxicity criteria for adverse events during HSCT. The main secondary end point was ability to discontinue immune-based medications and to decrease or discontinue antispasmodic medications. Other endpoints were quality of life assessments that included timed ambulation, Chronic Pain Acceptance Questionnaire (CPAQ), Barthel Index, Rankin Scale, and Short Form 36 (SF-36). Because there was heterogeneity in response to treatment, we descriptively correlate pre-HSCT features in relation to post-HSCT outcomes between the groups who were responders, defined as a continuous immune medication–free remission and at least a 50% decrease in antispasmodic medications; partial responders, defined as responded initially but then relapsed and needed further immune medications and/or restarting or increasing antispasmodic drugs; and nonresponders.

Statistical Methods

To avoid Bonferroni statistical errors that arise from data mining for pretransplantation factors that influenced outcome, data from multiple comparisons are presented as 95% confidence intervals (CIs) rather than p values. The 95% CIs for proportions involved calculations based on binomial distribution and were done separately for responders and nonresponders. These calculations were conducted in R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Unlike retrospective data mining of pre-HSCT variables that could affect response, the quality of life instruments were prospectively designed as outcome measures and are reported for the entire cohort and each group (responder, partial responder, and nonresponder) as p values assessed by the 2-tailed Student t test.

Data Availability

The protocol, statistical analysis, patient demographics, adverse events, and results will be available indefinitely at ClinicalTrials.gov (NCT02282514).

Results

Demographics

Fifty participants were referred, and 27 were excluded by phone or physical examination due to anti-GAD antibody negativity (n = 6), normal EMG (n = 5), other neurologic diseases (n = 5) (1 each of small fiber neuropathy, primary lateral sclerosis, amyotrophic lateral sclerosis, Parkinson disease, cervical 5–6 myelopathy), other medical complications (n = 3) (1 each of ankylosing spondylitis, common variable immune deficiency, primary pulmonary artery hypertension), no prior IVIG (n = 2), declined treatment (n = 2), denied insurance approval (n = 1), or amphiphysin positive (n = 3) (tables 1 and 2 and figure). Twenty-three participants were treated (22 on study, 1 compassionately) between May 2015 and August 2018 (shortest follow-up 18 months). Median follow-up was 3.6 years (range 1.5–4.5 years). All participants were initially misdiagnosed (table 1) as having other neurologic disorders (n = 7) (Parkinson disease, corticobasal degeneration, spinocerebellar atrophy, chronic inflammatory demyelinating polyneuropathy [n = 2], primary lateral

sclerosis, or hereditary spastic paresis), lumbar or cervical spinal disk disease (n = 4), seizures (n = 3), psychosomatic disorders (n = 2), and 1 participant each with frozen shoulder, temporal mandibular joint pain, sacroiliac joint pain, complications of spinal surgery, eosinophilic esophagitis, abdominal cramps, or migraine headache.

Participants had a mean age of 48 years (range 28–60 years), and most (21 of 23) were female.

CSF anti-GAD antibody was positive in 14 participants, negative in 6, and not checked in 3, while peripheral blood anti-GAD antibody was positive in all 23. Prior medications (and number of participants treated) were IVIG (n = 23), benzodiazepines (n = 23), corticosteroids (n = 9), rituximab (n = 9), plasmapheresis (n = 3), mycophenolate mofitel (n = 3), oral baclofen (n = 19), intrathecal baclofen (n = 2), antiseizure medications (n = 4), azathioprine (n = 4), calcineurin inhibitor (n = 2), methotrexate (n = 1), Botox (n = 5), and hydroxychloroquine (n = 2). Coexisting autoimmune diseases (and number of participants affected) included hypothyroidism (n = 12), Graves disease (n = 2), type 1 diabetes (n = 7), celiac disease (n = 1), goiter (n = 1), and vitiligo (n = 1). Twenty participants reported initiation of spasms by environmental stimuli of touch (n = 16), sound (n = 17), anxiety (n = 20), or bright light (n = 1). Twelve participants were afraid to leave their homes due to risk of paroxysmal spasms and falls. All participants were on IVIG before HSCT; other immune-suppressive/modulating drugs included rituximab (5 participants), plasmapheresis (2 participants), and cyclosporine, tacrolimus, azathioprine, and mycophenolate mofetil (1 participant each) (table 3).

Twelve participants had normal tendon reflexes; 11 had hyperreflexia; and 4 demonstrated involuntary resistance to examiner's movement of a joint, that is, lead pipe rigidity; 1 had hemidystonia of the left arm; and 1 had cerebellar ataxia (table 2). All participants had constant stiffness; 16 participants had paroxysmal intermittent muscle spasms; and 7 participants reported that muscle spasms were constant. Eighteen participants required assistance for ambulation: 3 needed a cane; 2 required bilateral canes or walking sticks; 6 needed a walker; 5 were in wheelchairs; and 2 were bedridden.

Toxicity

No participants died during or as a result of treatment. One participant with lead pipe rigidity who was bedridden and unable to speak because of laryngeal spasms before transplantation died 1 year after transplantation of respiratory arrest. Transplantation hospitalization grade 4 toxicities (and number of participants) were anorexia/vomiting (n = 2) and hyperglycemia (n = 1). Transplantation grade 3 toxicities were hypophosphatemia (n = 13), hyperglycemia (n = 5), hypokalemia (n = 4), hyponatremia (n = 1), febrile neutropenia (n = 13), hypotension (n = 3), hypertension (n = 2), dyspnea (n = 4), vasovagal episode (n = 1), abdominal pain (n = 1), epistaxis (n = 1), transaminitis (n = 1), and infections (diarrhea, *Clostridium difficile* [n = 1], port-a-catheter, *Acinetobacter ursingii* [n = 1], urinary tract infection, *Escherichia coli* [n = 1], and respiratory/rhinovirus [n = 1]).

Infections within the first year after transplantation were treated with oral antibiotics and were sinusitis (n = 2), pharyngitis (n = 1), upper respiratory tract infection/bronchitis (n = 4), and conjunctivitis (n = 1). The only secondary autoimmune disease was 1 case of hypothyroidism occurring 2 years after transplantation.

Outcome

Eleven participants responded, entered an IVIG and immune-suppression drug–free remission, and have not relapsed during the follow-up period of 18 months to 4.5 years (figure and tables 2 and 3). Stiffness persisted but decreased in severity, while sporadic spasms and startle responses disappeared, and benzodiazepine and baclofen were discontinued or markedly reduced (table 3). Before transplantation, 2 of these 11 participants required a cane to ambulate, 3 used a walker, 2 were in wheelchairs, and 1 was bedridden. At last follow-up, 1 participant who was previously in a wheelchair was able to ambulate with a walker, and 1 previously bedridden patient was able to walk with an assistance of 1 arm while all others were able walk independently.

Six participants responded by becoming immune drug free but relapsed and restarted immune-based therapy. One participant with cerebellar ataxia restarted treatment 6 months after transplantation. The other 5 participants relapsed from 1 to 2 years after transplantation (table 3). Despite relapsing, 3 participants retained a degree of improvement: 1 improved from a wheelchair to a walker, while 2 have continued to require no assistance to ambulate after transplantation despite using a walker or wheelchair before transplantation. Six participants remained on immune-modulating or -suppressive drugs, had no benefit from transplantation, and are classified as nonresponders (table 3).

While the majority of participants (17 of 23) benefit from HSCT and 11 of 23 remain in remission, some participants (6 of 23) had no beneficial response. There were no apparent differences in age, disease duration, sex, race, anti-GAD seropositivity, or paraspinal EMG results between responders and nonresponders (table 1). Compared to nonresponders, responders were more likely to have pretransplantation intermittent muscle spasms in contrast to constant muscle spasm (16 of 17 [94%], 95% CI between 0.73 and 0.99 vs 0 of 6 [0%], 95% CI between 0.00 and 0.39) and normal reflexes (12 of 17 [71%], 95% CI between 0.47 and 0.87 vs 0 of 6 [0%], 95% CI between 0.31 and 0.90). Compared to responders, nonresponders were more likely to have lead pipe rigidity (4 of 6 [66%], 95% CI between 0.24 and 0.94 vs 0 of 17 [0%], 95% CI between 0.00 and 0.23) and simultaneous contraction of agonist/antagonist limb muscles on EMG (4 of 6 [67%], 95% CI between 0.30 and 0.90 vs 1 of 17 [6%], 95% CI between 0.01 and 0.27). Before HSCT, the use of prescription serotonin selective receptor inhibitors (SSRIs) or serotonin and

Table 1 General Pretransplantation Demographics

Remission Duration, y	Age, y/Sex	Race	Time From dx, y	Startle Spasm[a]	Blood/CSF Anti-GAD[b]	Other AD	Pre-HSCT EMG Paraspinal[c]	Initial Diagnosis	Initial Symptom
Responder									
4.5	40 F	Asian	4	Yes	+/ND	hypoT	ND	Complex partial seizure	Abdominal spasms
4.5	46 F	W	5	Yes	+/−	hypoT	abnl	Frozen shoulder	Upper back spasms
4.5	54 M	W	6	Yes	+/−	—	abnl	TMJ syndrome	Jaw spasms
4.5	56 F	W	5	Yes	+/+	hypoT	abnl	Psychosomatic	Abdominal spasms
4.5	42 F	AA	3	Yes	+/+	T1D	ND	Psychosomatic	Leg spasms/stiffness
4.0	35 F	AA	4	Yes	+/+	—	abnl	Seizures	Stiff gait
3.0	28 F	W	6	Yes	+/+	T1D	abnl	Tonic-clonic seizures	Low back spasms
3.0	53 F	W	11	Yes	+/+	T1D, hypoT	ND	Sacroiliac joint pain	Low back pain spasms
3.0	47 M	W	7	No	+/+	TIID, goiter	abnl	Parkinson	Low back spasms
2.5	54 F	AA	7	No	+/+	Graves	abnl	Corticobasal degeneration	Left upper arm hemidystonia
1.5	56 F	W	17	Yes	+/+	T1D, hypoT, celiac	abnl	Herniated disks	Face, back, leg fasciculations/spasms
Partial responder									
0.5	57 F	W	2	Yes	+/+	T1D, hypoT, vitiligo	nl	Cerebellar ataxia/ spinocerebellar atrophy	Diaphragm spasms
1.5	40 F	W	13	Yes	+/ND	—	ND	Surgical complication	Left leg spasms
1.5	51 F	H	8	Yes	+/+	hypoT	abnl	Herniated disk	Low back pain/falls
1.0	59 F	W	20	No	+/+	—	abnl	Herniated disk	Low back spasms
2.0	50 F	W	6	Yes	+/+	hypoT	abnl	Eosinophilic esophagitis	Esophageal spams
1.0	60 F	W	5	Yes	+/ND	hypoT	ND	Abdominal cramps	Abdominal spasms
Nonresponder									
0	44 F	W	7	Yes	+/+	T1D, Graves	abnl	Disk cervical cord compression	Spasms to touch
0	27 F	Asian	8	Yes	+/−	—	abnl	CIDP/AAG	Loss of visual depth perception, abdominal spasms
0	53 F	W	4	No	+/−	hypoT	abnl	migraine	Upper back spasms/pain
0	57 F	W	5	Yes	+/+	hypoT	nl	Primary lateral sclerosis	Unilateral foot drag/clonus
0	55 F	W	5	Yes	+/−	—	abnl	CIDP	Numb/spastic legs
0	48 F	W	6	Yes	+/−	hypoT	abnl	Hereditary spastic paresis	Unilateral leg stumbling

Abbreviations: AA = African America; AAG = Autoimmune Autonomic Ganglionopathy; abnl = abnormal; AD = autoimmune disease; CIDP = chronic inflammatory demyelinating polyneuropathy; GAD = glutamic acid decarboxylase; HSCT = hematopoietic stem cell transplantation; hypoT = hypothyroidism; LBP = lead pipe rigidity; ND = not done; nl = normal; T1D = type 1 diabetes mellitus; TMJ = temporomandibular joint; W = white.
Responder is defined as a continuous immune medication–free remission and at least a 50% decrease in antispasmodic medications. Partial responder is defined as restarting immune medications and/or restarting or increasing antispasmodic drugs. Nonresponder is defined as inability to stop immune medications or to decrease antispasmodic medications.
[a] Startle response = spasms induced by touch or noise.
[b] All patients positive for anti-GAD antibody in the blood.
[c] Abnormal paraspinal EMG = continuous motor unit potential firing/inability to relax.

Table 2 Pretransplantation Characteristics That May Help Distinguish Response to Autologous HSCT

Remission Duration, y	Pretransplantation CNS and Spinal Surgeries	Pre-HSCT EMG of Limbs[a]	Pre-HSCT Muscle Spasms	Reflexes	LPR	Antidepressant
Responder						
4.5	None	nl	Intermittent	nl	No	0
4.5	None	nl	Intermittent	nl	No	0
4.5	None	nl	Intermittent	nl	No	0
4.5	None	nl	Intermittent	nl	No	0
4.5	None	nl	Intermittent	nl	No	0
4.0	None	nl	Intermittent	Knee +4, ankle clonus		0
3.0	Craniotomy for refractory seizures	nl	Intermittent	nl	No	0
3.0	None	abnl	Intermittent	nl	No	0
3.0	None	nl	Intermittent	nl	No	0
2.5	None	nl	Intermittent	nl/hemidystonia	No	0
1.5	L4–S1 spinal fusion	nl	Intermittent	nl	No	0
Partial responder						
0.5	Cervical spine fusion	nl	Intermittent	Knee +3, cerebellar ataxia	No	SNRI
1.5	C5-6 fusion, C4-5-6 laminectomy, C4-7 rods	nl	Continuous	Elbow +3, knee +3	No	SNRI/SSRI
1.5	L4-S1 surgery 3 times	nl	Intermittent	Knee +3,	No	SSRI
1.0	None	nl	Intermittent	nl	No	SNRI
2.0	None	nl	Intermittent	nl	No	SSRI
1.0	None	nl	Intermittent	Knee+3, elbow+3	No	0
Nonresponder						
0	Anterior cervical fusion	abnl	Continuous	Lower LPR	Yes	SNRI
0	None	abnl	Continuous	Knee +3	No	SNRI/SSRI
0	None	nl	Continuous	Knee +3, ankle clonus	No	SSRI
0	None	nl	Continuous	Knee +3, ankle LPR	Yes	0
0	None	abnl	Continuous	Upper/lower LPR	Yes	0
0	Thoracic T7-8 surgery 2 times	abnl	Continuous	Upper/lower LPR	Yes	SNRI

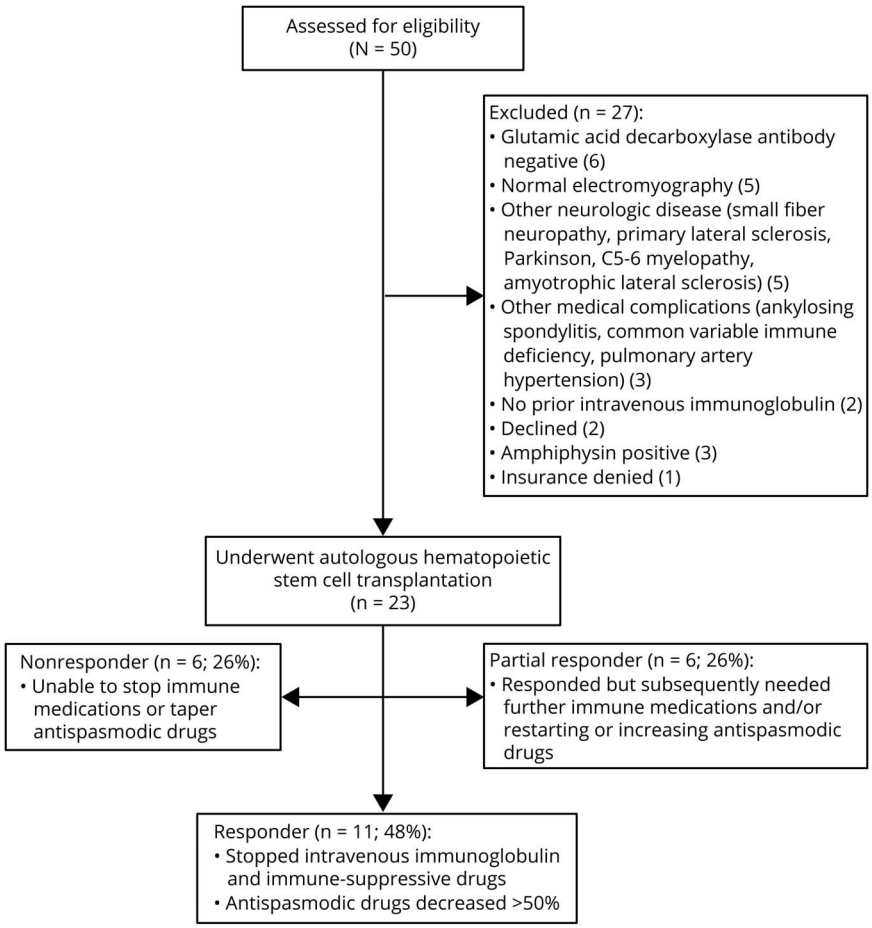
Abbreviations: abnl = abnormal; HSCT = hematopoietic stem cell transplantation; LPR = lead pipe rigidity; nl = normal; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = serotonin selective receptor inhibitor.
Responder is defined as a continuous immune medication–free remission and at least a 50% decrease in antispasmodic medications. Partial responder is defined as restarting immune medications and/or restarting or increasing antispasmodic drugs. Nonresponder is defined as inability to stop immune medications or to decrease antispasmodic medications.
[a] Abnormal limb EMG = simultaneous activation of agonist/antagonist (flexor/extensor) muscles in limb extremity.

norepinephrine reuptake inhibitors (SNRIs) was more common for those who relapsed or never responded (9 of 12 [75%], 95% CI between 0.00 and 0.26) compared to responders who never relapsed (0 of 11 [75%], 95% CI between 0.47 and 0.91). Due to participant uncertainty, duration of pretransplantation SSRI/SNRI use was not captured.

Anti-GAD Antibodies

Before HSCT, CSF anti-GAD antibodies before HSCT were positive in 12 of 14 (86%: 95% CI between 0.60 and 0.96) responders compared to 2 of 6 (33%: 95% CI between 0.10 and 0.70) nonresponders (table 1). After transplantation, CSF anti-GAD antibodies were not rechecked. All participants were

Figure Study Design



seropositive for blood anti-GAD antibodies before HSCT (table 1). Response to HSCT did not correlate with post-HSCT changes in blood anti-GAD antibody status (table 4).

Quality of Life

Quality of life indices included timed ambulation, CPAQ, Barthel Index, Rankin Scale, and SF-36. Timed ambulation was not a practical scale for this cohort because some participants were bedridden or in a wheelchair, which prevented an adequate baseline value, but subsequently improved or required no assistance after HSCT (documented in table 3). For those participants who could ambulate before HSCT, the responders improved their 25-ft walk from a mean pre-HSCT of 10.5 seconds to a mean at last follow-up of 5.7 seconds ($p = 0.09$) The mean of the responders who relapsed was 8.31 seconds before HSCT and 8.98 seconds at last follow-up (not significant). For nonresponders, the mean 25-ft walk before HSCT and at last follow-up was 10.51 and 10.47 seconds, respectively (not significant). The CPAQ demonstrated no significant change overall from a mean pre-HSCT value of 60.7 to 52.09 at last follow-up ($p = 0.19$). The mean CPAQ value from before HSCT and to last follow-up decreased from 62.6 to 49.18 ($p = 0.28$) for responders who did not relapse, changed from 49.5 to 43.3 ($p = 0.62$) for responders who relapsed, and changed from 70 to 67.6 ($p = 0.30$) for nonresponders. However, compared to the other groups, responders who did not relapse were able to discontinue or markedly decrease antispasmodic drugs (table 3) without an increase in pain.

From before HSCT to last follow-ups, the Barthel Index scores of the entire cohort did not improve significantly (83.4 and 88.8, respectively, $p = 0.11$). The Barthel Index scores of the responders and the responders who relapsed improved from before HSCT to last follow-up (85.9 to 95.9 [$p = 0.04$] and 75 to 83 [$p = 0.05$], respectively). The Barthel Index scores of the nonresponders worsened from before HSCT to last follow-up (88 to 80 [$p = 0.45$]). Rankin Scale scores from before HSCT to last follow-up improved significantly for the entire group (3.13 to 2.10 [$p = 0.004$]). The Rankin Scale scores of the responders and the responders who relapsed improved from before HSCT to last follow-up (3 to 1.5 [$p = 0.004$] and 3.3 to 2.5 [$p = 0.04$], respectively). The Rankin Scale score of the nonresponders worsened from before HSCT to last follow-up (3.2 to 3.3 [not significant]).

The SF-36 scores for the entire cohort and separately for responder, partial responder, and nonresponder in terms of physical component, mental component, and total score are

Table 3 Clinical Outcome

Remission Duration, y	Gait Before HSCT	Current Gait After HSCT	Spasms Before HSCT	Spasms After HSCT	Regular Immune Therapy Before HSCT	Immune Therapy After HSCT	Diazepam/ Baclofen Before HSCT, mg/d	Current Diazepam/ Baclofen, mg/d
Responder								
5.0	Cane/hold onto person	No assist	Hospitalization 2–3/mo	None	IVIG every 4 wk	None	10–100/0 IV propofol in hospital	2.5/0
4.5	Walker	No assist	10–20/d	None	IVIG every 2 wk solumedrol	2 doses rituximab at 1 y (reason unclear)	10/20	0/0
4.5	No assist	No assist	Daily	None	IVIG every 2 wk	None	60/10	0/0
4.5	Wheelchair	No assist	Frequent spasms	None	IVIG every 4 wk, rituxan every 6 mo	None	30/20	0/10
4.5	Wheelchair	Walker	Monthly	None	IVIG every 4 wk	None	90/10	5/0
4.0	Bedridden	Walk 1 arm assist	Hospitalization every 2 wk	None	IVIG every 3 wk, rituxan every 12 mo	None	45/45	10/5
3.0	Cane	No assist	3–4 times/d	1/mo	IVIG every 6 weeks, rituxan every 6 mo	None	20/pump	10/pump
3.0	Walker	No assist	2 times/d	None	IVIG every mo, CSA	None	20/0	2.5/0
3.0	No assist	No assist	daily	None	IVIG every mo, azathioprine	None	200/0	10/0
2.5	No assist	No assist	2 times/mo	None	IVIG every 2 wk	None	8/0	0/0
1.5	Walker	No assist	QOD, hospitalization every 3 mo	None	IVIG every mo	None	40/120	0/60
Partial responder								
0.5	Wheelchair	Walker	Multiple daily	None	IVIG every mo, PLEX every mo	Rituximab	40/20	10/0
1.5	Walker	No assist	Continuous	Restarted[a]	Rituxan/PLEX	Rituximab	90/45	90/60
1.5	Walker	walker	3 times/d	Restarted[a]	IVIG every 2 wk	IVIG	5/20	5/0
1.0	Wheelchair	No assist	Multiple weekly	Restarted[a]	IVIG intermittent	IVIG	60/30	60/30
2.0	No assist	wheelchair	1–5 times/d	Restarted[a]	IVIG every 2 wk	Rituximab	0[b]/30	0[b]/30
1.0	Walking sticks	Walking sticks	Multiple	No startle	IVIG every 4 wk	IVIG	5/0	5/0
Nonresponder								
0	Walker	Walker	Continuous	No change	IVIG intermittent	IVIG	60/pump	45/pump
0	Wheelchair	Wheelchair	Continuous	No change	IVIG every 2 wk	IVIG	20/0	[c]/0
0	No assist	cane	Continuous	No change	IVIG every 2 wk, tacrolimus, MMF	IVIG	0/30	15/90
0	Bilateral cane	Walker	Continuous	No change	IVIG every week, rituxan intermittent	IVIG, rituximab	10/0	10/0
0	Cane	Cane	Continuous	No change	IVIG intermittent	IVIG	Decline FU	No FU
0	Bedridden	Bedridden	Continuous	No change	IVIG every 2 wk	Hospice care	Died of disease 1 y	Deceased

Abbreviations: CSA = cyclosporin A; FU = follow-up; HSCT = hematopoietic stem cell transplantation; IVIG = IV immunoglobulin; MMF = mycophenolate mofetil; PLEX = plasma exchange.
Responder is defined as a continuous immune medication–free remission and at least a 50% decrease in antispasmodic medications. Partial responder is defined as restarting immune medications and/or restarting or increasing antispasmodic drugs. Nonresponder is defined as inability to stop immune medications or to decrease antispasmodic medications.
[a] Spasms disappeared after HSCT then restarted at time of relapse.
[b] Never used diazepam; treated with clonazepam dose unchanged.
[c] Decreased diazepam but added clonazepam and tizanidine.

Table 4 Clinical Outcome vs Peripheral Blood Anti-GAD Antibody Serologic Titer

Patient	Before HSCT, IU/mL	6 mo After HSCT, IU/mL	1 y After HSCT, IU/mL	2 y After HSCT, IU/mL
Responder				
1	>30	>30	>250	>250
2	2.5	<5	<5	<5
3	5.2	<5	<5	<5
4	>30	88	ND	104
5	>30	>250	ND	>250
6	>30	>250	>250	>250
7	>250	>250	>250	>250
8	>250	>250	>250	>250
9	>250	>250	>250	>250
10	>250	>250	>250	
11	>250	>250	ND	
Partial responder				
1	19.2	>250	>250	>250
2	>30	18.1	>250	125
3	>250	>250	>250	>250
4	>250	>250	ND	ND
5	>30	>250	>250	11,072
6	9.3	ND	2	100
Nonresponder				
1	>30	>30	>250	>250
2	105	75	156	143
3	116	85	104	0.08 nmol/L
4	>250	>250	ND	
5	6.3	0	ND	
6	64	Deceased		

Abbreviations: GAD = glutamic acid decarboxylase; HSCT = hematopoietic stem cell transplantation; ND = not done.
Responder is defined as a continuous immune medication–free remission and at least a 50% decrease in antispasmodic medications. Partial responder is defined as restarting immune medications and/or restarting or increasing antispasmodic drugs. Nonresponder is defined as inability to stop immune medications or to decrease antispasmodic medications.

reported in table 5. The SF-36 total score for the entire cohort improved from a pre-HSCT mean of 37.75 to a mean at last follow-up of 58.35 ($p = 0.0006$). The SF-36 total score for the responders who did not relapse improved from a pre-HSCT mean of 37.43 to a mean at last follow-up of 71.06 ($p = 0.001$). The SF-36 total score for the responders who relapsed improved from a pre-HSCT mean of 38.15 to a mean at last follow-up of 50.16 ($p = 0.08$). In contrast, the SF-36 total score for the nonresponders deteriorated from 37.97 before HSCT to 36.69 at last follow-up ($p = 0.67$). The significance in mental score and physical score was similar to that of the total score within each group (table 5).

Discussion

By tradition, whenever hematopoietic stem cells (HSCs) are infused after chemotherapy, the procedure is called a transplant. However, when transplantation is used in the term HSCT, the rationale for infusing the HSCs may be confused with the rationale for mesenchymal stem cell (MSC) or neural stem cell (NSC) transplantation. MSC and NSC transplantations are performed without a conditioning regimen (i.e., no chemotherapy or biologics) because these trials are instigated for an independent NSC neuroregenerative effect or a stand-alone MSC immunesuppressive effect. In comparison, HSCs, by themselves, have

Table 5 Quality of Life: Short Form 36 Scores

	Baseline	At 6 mo	Last Follow-Up
All patients[a]			
Physical score			
No. of patients	22	21	22
Median (IQR)	25.40 (22.1–32.2)	42.40 (30.0–58.0)	43.70 (31.4–70.3)
Mean (SD)	27.26 (10.84)	46.76 (20.77)	49.94 (24.78)
95% CI	22.45–32.07	37.31–56.21	38.85–60.93
***p* Value**		0.0007	0.0003
Mental score			
No. of patients	22	21	22
Median (IQR)	50.10 (34.9–58.8)	58.40 (37.6–76.0)	67.35 (57.4–83.0)
Mean (SD)	46.20 (17.14)	59.47 (23.11)	65.27 (20.54)
95% CI	38.6–53.8	48.95–69.99	56.16–74.38
***p* Value**		0.02	0.0014
Total score			
No. of patients	22	21	22
Median (IQR)	39.63 (27.3–47.6)	50.73 (32.3–71.2)	53.66 (47.4–76.3)
Mean (SD)	37.75 (12.81)	52.91 (22.76)	58.35 (22.81)
95% CI	32.07–43.43	42.55–63.27	48.24–68.46
***p* Value**		0.0068	0.0006
Responders			
Physical score			
No. of patients	11	11	11
Median (IQR)	26.20 (24.2–33.2)	46.80 (42.0–70.2)	70 (43.7–80.5)
Mean (SD)	29.11 (11.41)	53.60 (20.75)	63.56 (22.94)
95% CI	21.44–36.78	39.66–67.54	49.49–77.63
***p* Value**		0.014	0.002
Mental score			
No. of patients	11	11	11
Median (IQR)	40.0 (29.9–57.9)	68.03 (51.3–86.1)	75.7 (66.6–87.9)
Mean (SD)	42.42 (18.02)	66.54 (21.46)	74.60 (15.16)
95% CI	30.31–54.53	52.12–80.96	64.42–84.78
***p* Value**		0.028	0.002
Total score			
No. of patients	11	11	11
Median (IQR)	40.75 (25.1–48.6)	54.25 (45.8–80.3)	76.06 (53.6–85.8)
Mean (SD)	37.43 (12.94)	60.21 (22.01)	71.06 (17.9)
95% CI	28.74–46.12	45.42–74.99	59.03–83.09
***p* Value**		0.026	0.001
Partial responders			
Physical score			

Continued

Table 5 Quality of Life: Short Form 36 Scores *(continued)*

	Baseline	At 6 mo	Last Follow-Up
No. of patients	6	5	6
Median (IQR)	28.4 (19.6–37.0)	36.4 (29.8–56.4)	49.8 (19.7–63.8)
Mean (SD)	27.13 (13.31)	42.68 (24.14)	43.03 (26.74)
95% CI	13.16–41.1	12.71–72.65	14.97–71.09
***p* Value**		0.158	0.05
Mental score			
No. of patients	6	5	6
Median(IQR)	49.55 (44.8–66.2)	37.6 (36.8–68.8)	61.65 (45.2–79.4)
Mean (SD)	50.27 (21.04)	50.12 (29.54)	58.28 (26.34)
95% CI	28.19–72.35	13.44–86.8	30.64–85.92
***p* Value**		0.614	0.264
Total score			
No. of patients	6	5	6
Median (IQR)	37.97 (32.8–51.2)	32.38 (31.2–71.2)	56.78 (33.-71.27)
Mean (SD)	38.15 (17.43)	44.5 (27.96)	50.61 (26.05)
95% CI	19.86–56.44	9.78–79.22	23.27–77.95
***p* Value**		0.361	0.081
Nonresponders[a]			
Physical score			
No. of patients	5	5	5
Median (IQR)	24.40 (21.4–27.6)	30.0 (29.4–40.2)	29.2 (21.4–30)
Mean (SD)	23.36 (6.45)	35.8 (14.09)	28.24 (7.99)
95% CI	15.35–31.37	18.3–53.3	18.32–38.16
***p* Value**		0.038	0.096
Mental score			
No. of patients	5	5	5
Median (IQR)	50.8 (49.4–52.1)	64.0 (36.7–64.0)	57.4(40.6–58.1)
Mean (SD)	49.67 (9.92)	53.27 (18.73)	53.15 (16.62)
95% CI	37.35–61.99	29.97–76.49	32.51–73.79
***p* Value**		0.569	0.449
Total score			
No. of patients	5	5	5
Median (IQR)	40.83 (35.5–42.6)	48.71 (33.1–50.6)	40.5 (33.6–48.71)
Mean (SD)	37.97 (7.93)	45.24 (16.96)	39.69 (10.66)
95% CI	28.12–47.82	24.18–66.3	26.45–52.93
***p* Value**		0.246	0.667

Abbreviations: CI = confidence interval; IQR = interquartile range.
Responder is defined as a continuous immune medication–free remission and at least a 50% decrease in antispasmodic medications. Partial responder is defined as restarting immune medications and/or restarting or increasing antispasmodic drugs. Nonresponder is defined as inability to stop immune medications or to decrease antispasmodic medications.
[a] One nonresponder, who was bedridden with lead pipe rigidity of all extremities before HSCT, did not return and died 1 year after HSCT of disease progression.

no beneficial or clinical stand-alone neuroregenerative or immune-suppressive effect. HSCs are infused for their normal homologous purpose, that is, a blood transfusion support to hasten recovery of hematopoiesis after chemotherapy and biologics (conditioning regimen). Toxicity and efficacy of autologous HSCT arise from the immune-suppressive conditioning regimen and participant selection, not the autologous HSCs per se.

SPSD is a rare but disabling neurologic disorder that is often misdiagnosed. Initial symptoms of classic SPSD are leg stiffness followed by paraspinal muscle rigidity and spasms. Subsequently, over several years, the ability to walk independently is lost.[26] Treatment is based on muscle relaxants and modulation or suppression of the immune system. IVIG has been reported to improve the stiffness score in a randomized trial of 16 participants, but symptoms rebounded when IVIG was discontinued.[17] Rituximab, a B lymphocyte (CD20)–depleting antibody, is commonly used to treat SPSD and has been reported to be beneficial[18–20] but failed in a randomized trial compared to placebo.[21] The lack of efficacy of rituximab was contributed to the small number of participants and insensitivity of the stiffness scale.[21]

When the current trial was designed, there was no literature roadmap to follow on the risks and benefit of HSCT for SPS. We therefore undertook a phase I/II safety study of HSCT for SPS. After enrolling 23 participants, even though there had been no treatment-related or unexpected deaths, we noted that a large proportion did not respond or had only a short-term response; therefore, we voluntarily halted enrollment but continued to follow up treated participants. The decision was based on our duty as a research team to carefully assess the balance between the predictable risks and burdens against any foreseeable benefit. At the time of terminating enrollment, we were unable to predict a priori who would or would not respond to treatment, and we did not want to expose participants who would not benefit to the short- and long-term risks of high-dose chemotherapy.

In MS, HSCT-related mortality in the European Bone Marrow Transplantation registry data has progressively decreased from 7.3% between 1995 and 2000 to 1.3% between 2001 and 2007, to 0.7% between 2008 and 2016, and subsequently to the most recently reported level of 0.2% (1 of 439 for 2012–2016).[27] The decline in mortality over time has been due in part to the realization that the more disabled and higher-risk secondary progressive form of MS does not benefit from HSCT, resulting in a shift toward selection of patients with relapsing remitting MS with frequent relapses who are less disabled and who demonstrate benefit from HSCT.[27–29] Drawing on this experience, we felt that it was important to stop enrollment in this study and to follow up participants to determine whether, similar to the history of HSCT for MS, we could identify factors that would indicate beneficial response to treatment.

The IVIG study of SPS enrolled a total of 16 participants, and the response was judged by the Stiffness Index and the Heighten Sensitive Scale while remaining on IVIG and antispasmodic treatments. The goal of HSCT, unlike other immune-based therapies, is to improve and remain free from all immune-modulating or -suppressive drugs and, in the case of SPS, all antispasmodic therapy. To this end, the efficacy endpoint after HSCT is the duration of time that participants remain immune therapy free while also tapering their antispasmodic drugs. During the post-HSCT period, either the local neurologist or the study neurologist could restart any immune or antispasmodic therapy when clinically needed. Therefore, the outcome measure used in this study is more stringent than that used in other studies, which depended on detecting changes in a stiffness score while continuing immune-based and antispasmodic therapies.

Because of the unexpected results that some participants responded and others did not, after allowing time for results to mature, we data mined to identify any pretransplantation factors that were different between responders and nonresponders. In addition, when we calculated outcome factors such as the SF-36 score, we noted that quality of life improved significantly for the entire cohort, which, if published as such, would be misleading. The aim of this article is therefore to demonstrate the heterogeneity in response and to investigate whether any pre-HSCT factors could predict who would and who would not respond to HSCT. This is important not only to better understand the pathophysiology clinical course of the disease but also to inform physicians so that participants who are unlikely to respond are not offered the risks of high-dose chemotherapy used in HSCT.

Limitations to retrospective data mining to predict outcome are that dependent covariables may appear individually significant when in fact they are not. For example, both hyperreflexia and prior SNRI and SSRI drugs were associated with a worse outcome. However, SNRI/SSRI drugs may themselves contribute to hyperreflexia. Because of overlapping covariables, the limited number of total participants, and retrospective data mining for pre-HSCT factors, which may affect outcome, we chose to present CIs rather than p values. These results, while not definitive, provide important information about this ultrarare disease and limitations to consider before offering aggressive immunosuppressive therapy, that is, autologous HSCT, to participants with SPSD. Acknowledging these caveats, the beneficial effect of HSCT was confined mostly to a phase of disease manifest by episodic spasms, normal reflexes, and continuous paraspinal motor unit activation. In contrast, HSCT was generally less effective once spasms became continuous, reflexes were hyperactive, and there was simultaneous cocontraction of limb agonist/antagonist muscles. No participant (0 of 4) with lead pipe rigidity responded to HSCT.

There was no correlation between anti-GAD antibodies in the peripheral blood and response. Anti-GAD titer has not been shown to correlate with disease severity,[9] response to rituximab,[30] or response of 2 participants with SPSD treated with a

more aggressive myeloablative HSCT regimen consisting of cyclophosphamide and busulfan.[31] We also did not observe a correlation with disease duration, but we have previously found in another neuroimmune disorder, MS, that response to autologous HSCT correlates to disease stage, that is, relapsing-remitting vs secondary progressive, rather than duration of disease per se.[32]

Participants who did not respond or relapsed tended to be on SSRI or SNRI antidepressants before HSCT. It has previously been reported that clomipramine, a tricyclic antidepressant, exacerbates SPSD symptoms when injected intravenously,[33] and oral SNRI antidepressants have also been reported to exacerbate SPSD.[34] However, in our study, the duration of exposure to different SSRI or SNRI antidepressants was not captured, and while there have been prior case reports of antidepressants exacerbating SPSD,[30,35] to the best of our knowledge, no large study has confirmed an association between serotonin reuptake inhibitors and SPSD. Participants demonstrating simultaneous cocontraction of agonist/antagonist limb muscles on EMG also did worse. However, the frequency of cocontraction of opposing limb muscle groups fluctuates and may be mitigated by adequate GABA enhancers such as baclofen or diazepam. In contrast, paraspinal muscle spasms that manifest as stiffness tend to be more persistent, as demonstrated in this cohort of participants.

No participant had the PERM variant of SPSD, and although falls and poor balance from paraspinal spasms were common symptoms, only 1 participant had the cerebellar variant of SPSD. Cerebellar SPSD tends to be refractory to immune-based therapies,[36] and the participant relapsed within 6 months of HSCT, but the improvement from wheelchair to walker was maintained on intermittent maintenance rituximab. It is impossible, however, to draw conclusions about response of cerebellar ataxia from a single participant. Because an imbalance in neural energy supply due to depletion from chronic neuronal activation may in theory lead to persistent neuronal dysfunction or degeneration[35] and because autopsies performed in the later stages of SPSD have been reported to demonstrate neuronal loss,[14–16] it is speculative, but unproven, that a subset of individuals with SPSD may have a pathophysiology that is relatively unresponsive to immune-based therapies. The results presented herein are consistent with a subset of SPSD unresponsive to autologous HSCT, an aggressive immune therapy–directed intervention.

To help clarify responders from nonresponders, future studies may consider magnetic resonance spectroscopy,[7] EMG exteroceptive and pharmacologic testing,[33] or a tissue-based CSF anti-GAD functional assay. While MRI is generally normal in participants with SPSD, GABA is diminished within the CNS on magnetic resonance spectroscopy.[7] EMG findings such as an abnormal exteroceptive response or response to neuropharmacologic testing are not routinely performed by our EMG laboratory but could be evaluated as possible predictors of outcome to HSCT.[34] A successful tissue-based functional assay for anti-GAD has not, to the best of our knowledge, been developed and standardized. In fact, injection of anti-GAD antibodies into a rat hippocampus did not alter GABAergic transmission, which is consistent with the findings presented herein that anti-GAD antibodies did not correlate with clinical outcome.[37]

This pilot study has helped to define a subset of participants with SPSD who are likely to respond to autologous HSCT while also raising concerns about an immune-nonresponsive subset of participants. Failure of blood anti-GAD antibody to correlate with clinical response suggests that it should not, by itself, be interpreted as a biomarker of disease activity.

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Richard K. Burt, MD	Northwestern University, Chicago, IL	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Roumen Balabanov, MD	Northwestern University, Chicago, IL	Interpreted the data; revised the manuscript for intellectual content
Xiaoqiang Han, MD	Northwestern University, Chicago, IL	Major role in the acquisition of data; analyzed the data; interpreted the data; revised the manuscript for intellectual content
Kathleen Quigley, RN	Northwestern University, Chicago, IL	Major role in the acquisition of data; revised the manuscript for intellectual content
Indira Arnautovic, MD	Northwestern University, Chicago, IL	Major role in the acquisition of data; analyzed the data; drafted the manuscript for intellectual content
Irene Helenowski, PhD	Northwestern University, Chicago, IL	Analyzed the data, performed statistical analysis
John Rose, MD	University of Utah, Salt Lake City	Revised the manuscript for intellectual content
Teepu Siddique, MD, PhD	Northwestern University, Chicago, IL	Interpreted the data; revised the manuscript for intellectual content

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