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Therapeutic plasma exchange in the management of stiff person syndrome spectrum disorders: a case series and review of the literature

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Nicolas Mercure-Corriveau*, Shuvro Roy*, Chen Hu, Elizabeth P. Crowe, Xianming Zhu, Danielle Obando, Eshan U. Patel, Aaron A. R. Tobian, Yujie Wang, Evan M. Bloch† and Scott D. Newsome†

Abstract

Background: Stiff person syndrome spectrum disorders (SPSD) are a rare group of disabling neuroimmunological disorders. SPSD often requires immune therapies, especially in the setting of inadequate response to symptomatic treatments. The safety and efficacy of therapeutic plasma exchange (TPE) in SPSD remains uncertain.

Objectives: To describe the safety, tolerability, and efficacy of TPE in patients with SPSD.

Design: A retrospective observational study.

Methods: A retrospective review of SPSD patients seen at Johns Hopkins Hospital (JHH) from 1997 to 2021 was performed. Patient demographics/history, examination/diagnostic findings, treatment response, and TPE-related complications were recorded. Assessment for any associations between clinical characteristics, including age, sex, clinical phenotype, and time on immunotherapy, and response to TPE 3 months after treatment was performed. A subgroup of 18 patients treated with TPE at JHH and 6 patients treated with TPE at outside institutions were evaluated for any change in usage of symptomatic medications 3 months after the TPE treatment. Literature review of SPSD and TPE was also conducted.

Results: Thirty-nine SPSD patients were treated with TPE (21 at JHH and 18 at outside institutions); median age 48 years, 77% female, median modified Rankin Scale 3; mean initial anti-GAD65 antibody titer was 23,508 U/mL. Twenty-four patients (62%) had classic SPS, 10 (26%) had SPS-plus, 2 (5%) had progressive encephalomyelitis with rigidity and myoclonus, and 3 (8%) had pure cerebellar ataxia. All patients were on symptomatic treatments, 30 (77%) previously received IVIg, and 3 (8%) previously received rituximab. Four patients (10%) had a TPE-related adverse event. One developed asymptomatic hypotension, another had both line thrombosis and infection, and two had non-life-threatening bleeding events. Twenty-three (59%) patients reported improvement in symptoms after TPE. Of the subgroup of 24 patients evaluated for any change in usage of symptomatic medications 3 months after the TPE treatment, 14 (58%) required fewer GABAergic symptomatic medications. Literature review identified 57 additional patients with SPSD; 43 (75%) reported temporary improvement after TPE.

Conclusion: The majority of patients treated with TPE had improvement. Moreover, most patients evaluated for any change in usage of symptomatic medications after the TPE treatment no longer required as much symptomatic medications months after TPE. TPE appears safe and well-tolerated in SPSD. Further studies are needed to assess the long-term efficacy of TPE in SPSD and identify which patients may benefit the most from TPE.

Keywords: GAD65, stiff person syndrome, therapeutic plasma exchange

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Correspondence to:
Scott D. Newsome
Division of Neuroimmunology and Neurological Infections, Department of Neurology, Johns Hopkins University, School of Medicine, 600 North Wolfe Street, Pathology 627, Baltimore, MD 21287, USA.
snewsom2@jhmi.edu

Nicolas Mercure-Corriveau
Elizabeth P. Crowe
Xianming Zhu
Eshan U. Patel
Aaron A. R. Tobian
Evan M. Bloch
Division of Transfusion Medicine, Department of Pathology, School of Medicine, Johns Hopkins University, Baltimore, MD, USA

Shuvro Roy
Chen Hu
Division of Neuroimmunology and Neurological Infections, Department of Neurology, Johns Hopkins University, School of Medicine, Baltimore, MD, USA

Danielle Obando
Department of Neurology, Johns Hopkins University, School of Medicine, Baltimore, MD, USA

Yujie Wang
Department of Neurology, Johns Hopkins University, School of Medicine, Baltimore, MD, USA

Department of Neurology, University of Washington, Seattle, WA, USA

*N.M.-C. and S.R. contributed equally to this work.

†E.M.B. and S.D.N. contributed equally to this work.

Introduction

Stiff person syndrome spectrum disorders (SPSD) are a group of rare neurological disorders that are most commonly characterized by axial and limb rigidity with superimposed painful muscle spasms. The symptoms of SPSD may be profound and functionally debilitating. SPSD is twice as common in women as it is in men and typically affects middle-aged individuals.[1] The presentation of SPSD is heterogenous and varies based on the phenotype as follows: classic, partial, SPS-plus, pure cerebellar ataxia (CA), progressive encephalomyelitis with rigidity and myoclonus (PERM), and overlapping syndromes.[2] In a large retrospective study of 212 anti-glutamic acid decarboxylase 65 (GAD65) neurological autoimmunity samples identified (out of greater than 380,000 samples submitted) and examined at the Mayo Clinic laboratory from 2003–2018, only approximately a third of cases were categorized as having SPSD.[3] Due to its rarity, little is known about the true incidence of SPSD, its spectrum of presentation, and importantly its ideal management.

To date, there are no consensus guidelines to help clinicians determine how to treat people with SPSD. Symptomatic interventions are often used as the cornerstone of treatment; however, many patients with SPSD will eventually be treated with an immune-based therapy. Among the symptomatic therapies, benzodiazepines and baclofen are widely considered first-line agents to manage SPSD, although no controlled studies have been conducted. These agents are associated with dose-related adverse effects, including sedation and cognitive slowing. When symptomatic therapies do not offer satisfactory therapeutic benefits, patients are treated with immunotherapy, of which intravenous immunoglobulin (IVIg) is most commonly used. IVIg demonstrated in a placebo-controlled, cross-over trial to help improve patients' mobility and function.[4] In cases that are unresponsive to IVIg, rituximab has been used with varying success.[5]

Clinical studies have evaluated the use of combination therapies that include standard pharmacological symptomatic therapies coupled with cognitive-behavioral therapy (CBT), IVIg, and therapeutic plasma exchange (TPE).[6] However, the role of TPE in SPSD is not well characterized. In general, TPE involves the removal of plasma containing pathologic mediators (e.g., antibodies) and the subsequent replacement of the removed plasma with normal saline, 5% albumin, and/or donor plasma. Since its first clinical use in 1952 (to treat a patient with hyperviscosity syndrome due to Waldenstrom Macroglobulinemia), TPE has been used to treat diverse conditions including neurological diseases.[7,8] TPE is a Category III indication for SPSD suggesting that, 'optimum role of apheresis therapy is not established, whereby decision making should be individualized', according to the American Society for Apheresis (ASFA).[8] Furthermore, SPSD is a Grade 2 C indication, reflecting a weak recommendation with low-quality evidence to support practice that has largely been gleaned from case reports or small case series.[9,10] Given the paucity of data surrounding TPE in SPSD, we sought to characterize the patient population managed at Johns Hopkins Hospital (JHH) who underwent TPE as part of their clinical management of SPSD to contextualize the role of TPE and describe the safety, tolerability, and treatment effect in those who received TPE. We also conducted a literature review pertaining to TPE and SPSD cases to complement our findings.

Methods

Study design

We conducted a retrospective review of all patients with a diagnosis of SPSD who were seen at JHH from 1 January 1997 to 30 May 2021 who had been treated with TPE. Cases were identified through two separate databases and cross-referenced for accuracy: the Johns Hopkins SPS Center longitudinal observational cohort database and the JHH Hemapheresis and Transfusion Support (HATS) database. We identified 39 total cases, with 21 patients receiving their TPE at JHH, and 18 receiving their TPE elsewhere. This study was approved by the JH Institutional Review Board (IRB), and all participants provided consent as part of an ongoing, longitudinal observation study.

A diagnosis of SPSD was determined by an SPSD expert clinician (S.D.N.) at JHH based on a combination of the following characteristics: (a) clinical presentation, including typical body regions involved (torso and lower extremities > upper extremities) for classic phenotype; classic features plus brainstem and/or cerebellar involvement for SPS-plus phenotype; pure cerebellar involvement for pure

cerebellar phenotype (these patients were included under SPSD as many will eventually develop additional symptoms consistent with SPS-plus or PERM); exclusively one limb involved for partial SPS; PERM as described in other publications[2]; (b) hallmark triggers for spasms/increased rigidity (abrupt loud noises, cold weather, open spaces, emotional stressors, or tactile stimuli); (c) hallmark examination findings, including hyperlordosis, paravertebral/abdominal spasms/rigidity, spasticity in extremities or hyperreflexia, brainstem/cerebellar signs, myoclonus among other findings as noted in prior publications[2]; (d) high-titer serum autoantibodies to GAD65, or the presence of glycine receptor or amphiphysin antibodies[11,12]; and (e) exclusion of alternative diagnoses and better explanation to account for the findings.

Commercially available autoantibody testing was used as part of standard clinical practice in the care of these individuals. The clinical laboratories included, for the anti-GAD65 antibody, were Johns Hopkins (utilizing Enzyme Linked Immunoassay [ELISA] method), Quest Laboratories (utilizing ELISA method), and Mayo Clinic Laboratories (utilizing Radioimmunosassay [RIA] method). For the ELISA method, values at or above 10,000 IU/mL were designated as high, and for the RIA method, the value was at or above 20 nmol/mL. For the anti-amphiphysin and anti-glycine receptor antibody, the Mayo Clinic Laboratories was used based on clinical suspicion. In addition, glycine receptor antibody testing was not commercially available until August 2020.

Variables

The following clinical and laboratory variables were collected for the study: demographic information (age, sex, race/ethnicity), clinical characteristics (e.g., symptoms and distribution of symptoms/findings, symptomatic triggers, exam findings, modified Rankin Scale [mRS]), medical comorbidities (e.g., diabetes, cancer), laboratory data (antibody test results and titer if applicable), symptomatic (gamma-Aminobutyric acid agonist [GABA] medications including benzodiazepines, baclofen, etc.) and immune treatments (IVIg, rituximab, mycophenolate mofetil, azathioprine, etc.), and electrophysiological studies. Data that were collected for TPE procedures included the timing of treatment in relation to onset of symptoms, the number of treatments, as well as previous treatment with IVIg or rituximab.

TPE procedures at JHH

All TPE procedures done at JHH were performed using either COBE® Spectra (Terumo BCT, Lakewood, CO) or Spectra Optia (Terumo BCT). The primary indication for TPE was acute worsening of SPSD or unresponsive/subtherapeutic response to initial immune therapy. For acute SPSD exacerbations, the treatment plan comprised of a series of TPE – a total of five procedures on alternating days. One plasma volume was exchanged per apheresis treatment. The procedure was typically undertaken using either central vascular access or less commonly using peripheral venous catheters. Human serum 5% albumin or a combination of 5% albumin with normal saline was used as replacement fluid for all procedures because the patients were not at high risk for bleeding. Acid citrate dextrose (ACD) was used as the anticoagulant in all procedures.

Vital signs were assessed by an apheresis nurse before starting the procedure as well as every 15–30 min throughout the procedure. The patient's clinical condition was also assessed before and during the procedure. Specifically, the apheresis nurse was monitoring for the following signs and symptoms: paresthesias, muscle cramps, dizziness, pruritus, and difficulty breathing. In addition, the venous catheter was examined before each procedure to ensure that it was functional and that there were no signs of infection or thrombosis.

TPE procedures performed outside of JHH were extracted with detailed chart review of patient's clinical notes (inpatient and outpatient records). Each patient's tolerability and responses to treatment were collected as documented in medical records.

TPE adverse effects

Possible complications related to the use of central venous access, anticoagulation, and replacement fluids were monitored closely and reported. Any change in vital signs or clinical status of the patient during a procedure was evaluated as a possible TPE-associated adverse event.

Clinical outcomes

The clinical responses were categorized as 'improved', 'no response', or 'worsened', as reported in clinical notation by the patient. A subgroup of 24 patients who had available GABAergic medication status both before and after TPE (18 patients treated with TPE at JHH and 6 patients treated with TPE at outside institutions) were evaluated for any change in usage of symptomatic medications; this was determined by a reduction in either the dose or total number of GABAergic symptomatic medications during assessment at 3 months after TPE. We also reviewed the patient charts for any change in the mRS comparing their scores at their evaluation prior to TPE with that 3 months after TPE. This same group of patients was also assessed for any improvement in their gait after treatment with TPE, as assessed by either a physician or physical therapist during the time of their hospitalization or subsequent outpatient appointment.

Statistical analysis

Statistical analyses were performed using STATA version 13 (StataCorp, College Station, TX). Demographic, clinical, and laboratory characteristics were summarized for all 39 patients. Comparisons of TPE responses and medication reduction by patient characteristics were performed for a subgroup of 24 patients who had available GABAergic medication status both before and after TPE (18 patients treated with TPE at JHH and 6 patients treated with TPE at outside institutions) using *t*-test or Kruskal–Wallis test for continuous variables as appropriate, and Fisher's exact test for categorical variables. Logistic regression was performed to assess for any associations between clinical characteristics, including age, sex, clinical phenotype, and time on immunotherapy (evaluated based on time in days as well as greater than 6 months) and response to TPE as defined by a clinical response of 'improved', as well as with any reduction in GABAergic medications 3 months after treatment. Due to a small sample size, patient phenotypes were characterized into 'SPS', and 'Other', with the 'Other' category including patients with SPS-plus, CA, and PERM. We defined statistical significance as two-tailed $p < 0.05$.

Literature review

We performed a scoping review of the literature to assess the current status of knowledge pertaining to the use of TPE to treat patients with SPSD. A PubMed search was conducted using the following terms alone or in combination: 'therapeutic plasma exchange', 'plasmapheresis', 'stiff person syndrome spectrum disorders', 'stiff limb syndrome', 'stiff person syndrome', 'pure cerebellar ataxia', and 'progressive encephalomyelitis with rigidity and myoclonus'. This was extended to a Google search of similar combinations of the same terms. We reviewed all English-language articles published from 1 January 1980 through 30 June 2022. To ensure the capture of all information, we cross-referenced the bibliographies of reviewed articles. One study, by Pagano *et al.*,[13] was a case series of patients with SPSD treated with TPE, and includes patients treated at JHH who are included in this study.

Results

Patient demographic and clinical characteristics

A total of 39 patients underwent TPE between 1997 and 2021, with 21 of those patients receiving their TPE treatment at JHH. The average age was 48 years ($SD \pm 14$), 30 (77%) were female, 11 (28%) had diabetes, 2 (5%) had paraneoplastic-related SPS, and 36 (92%) were positive for serum anti-GAD65 antibodies (Table 1 and Supplementary Table 1). In total, 24 patients had classic SPS, 10 had SPS-plus, 2 had PERM, and 3 had CA. The median pre-TPE mRS was 3 [interquartile range (IQR) 3–4].

Before starting TPE, 30 (77%) patients had received IVIg, 3 (8%) patients had been treated with rituximab, and 2 (5%) with mycophenolate mofetil. Thirty-one (79%) patients started at least one additional immunotherapy after TPE; 24 (62%) patients started rituximab, 7 (18%) started IVIg, 4 (10%) started mycophenolate mofetil, and 2 (5%) started azathioprine. Six of the aforementioned patients were treated with multiple post-TPE immunotherapies. The remaining eight patients continued their pre-TPE immunotherapies (six IVIG, two rituximab). The indication to start TPE was for worsening of symptoms despite treatment with symptomatic medications and

first-line immune therapies. A smaller subset of four patients were treated chronically with TPE after their initial course, with timing of treatment guided by their clinical response. Other characteristics can be seen in Table 1.

Safety and tolerability of TPE

Four (10%) patients had an adverse event related to their course of TPE (Supplementary Table 2). All patients had a diagnosis of classic SPS and their age ranged from 32 to 59 years. One developed asymptomatic hypotension, another had both line thrombosis and line infection, and two had non-life-threatening bleeding events. Among patients who experienced adverse effects, one patient had a diagnosis of insulin-dependent diabetes but the other three had no medical comorbidities. There were no anaphylactic reactions or deaths.

Efficacy of TPE

Of the 39 patients who were treated with TPE, the majority ($n = 32$) were treated with a single TPE course (median: five procedures), and 23 (59%) had improvement in symptoms after TPE (Table 2). Of the 24 patients who had available GABAergic medication status both before and after TPE, 14 (58%) required less GABAergic medication 3 months after treatment as compared with their pre-treatment regimen. Furthermore, 12 (50%) patients of this subgroup who had available GABAergic medication status both before and after TPE exhibited improvement in their gait after treatment. Of the 21 patients who had available mRS both before and after TPE, 3/21 (14%) had an improved mRS 3 months later, 17/21 (81%) demonstrated no change, and 1/21 (5%) had a worsened mRS. The median pre-TPE mRS was 3 (IQR 3–4), and the median post-TPE mRS was 3 (IQR 3–4). There was no significant difference in mean mRS, with mean pre-TPE mRS of 3.44, and mean post-TPE mRS of 3.32 (-0.12 ± 0.27, $p = 0.66$).

When separately examining all patients for prognostic factors to TPE response by univariable analysis, there were no factors among age, sex, clinical phenotype (SPS, Other), and time on immune therapy (evaluated based on time in days as well as greater than 6 months), that were associated with symptomatic improvement (Table 2). The same was true when evaluating the same characteristics for any univariate association with reduced symptomatic therapy requirements when evaluated 3 months after TPE treatment (Table 3). Although, responders were on average 7 years younger than non-responders (45 *versus* 52 years,

Table 1. Overall characteristics of patients with SPSD seen at Johns Hopkins.

Characteristics	Overall, $n = 39$
Female, *n* (%)	30 (77)
Median age at TPE treatment, years (range)	48 (19–69)
Median pre-TPE anti-GAD65 titer, IU/mL (range)	18,960 (0–235,250)
Median post-TPE anti-GAD65 titer, IU/mL (range)	6,085 (4.3–107,725)
Median mRS (IQR)	3 (3–4)
Diabetes, *n* (%)	10 (26)
Cancer, *n* (%)	8 (21)
Race/ethnicity, *n* (%)	
White	19 (49)
Black	16 (41)
Hispanic	2 (5)
Asian	1 (3)
Other	1 (3)
Clinical phenotype, *n* (%)	
Classic SPS	24 (62)
SPS-plus	10 (25)
PERM	2 (5)
Cerebellar ataxia	3 (8)
Concurrent immune therapy, *n* (%)	35 (90)
IVIg	30 (77)
Rituximab	3 (8)
Mycophenolate mofetil	2 (5)
Time on immune therapy at time of TPE in months (range)	13.9 (0–116)

Median (interquartile range) for continuous variables; *n* (%) for categorical variables.
GAD, glutamic acid decarboxylase; IQR, interquartile range; IVIg, intravenous immunoglobulin; mRS, modified Ranking Scale; PERM, progressive encephalomyelitis with rigidity and myoclonus; SPS, stiff person syndrome; SPSD, stiff person syndrome spectrum disorders; TPE, therapeutic plasma exchange.

Table 2. Predictors of response to TPE in patients with SPSD.

	Overall	TPE response = no effect/worsened	TPE response = improved	*p* value
N	39	16	23	
Age, mean years (± *SD*)	48 (± 14)	52 (± 14)	45 (± 14)	0.14[a]
Sex = female, *n* (%)	30 (76.9)	14 (87.5)	16 (69.6)	0.36[a]
Phenotype, *n* (%)				0.66[b]
SPS	24 (61.5)	8 (50.0)	16 (69.6)	
Other[c]	14 (35.9)	7 (43.8)	7 (30.4)	
Duration of immune therapy at time of TPE onset > 180 days, *n* (%)	17 (44.7)	6 (37.5)	11 (50.0)	0.66[b]
Duration of immune therapy at time of TPE onset in days (median [IQR])	75 [0, 504]	0 [0, 572]	161 [0, 468]	0.45[d]

IQR, interquartile range; PERM, progressive encephalomyelitis with rigidity and myoclonus; *SD*, standard deviation; SPS, stiff person syndrome; SPSD, stiff person syndrome spectrum disorders; TPE, therapeutic plasma exchange.
[a]Two-tailed *t*-test.
[b]Fisher's Exact test.
[c]Kruskal–Wallis test.
[d]SPS-plus, Cerebellar ataxia, PERM (%).

Table 3. Predictors of symptomatic medication reduction after TPE in patients with SPSD.

	Overall	Post-TPE decrease = no	Post-TPE decrease = yes	*p* value
N	24	10	14	
Age, mean years (± *SD*)	46 (± 16)	50 (± 13)	44 (± 16)	0.30[a]
Sex = female, n (%)	19 (79.1)	8 (80.0)	11 (78.6)	1.00[a]
Phenotype, n (%)				0.88[b]
SPS	16 (66.7)	6 (60.0)	10 (71.4)	
Other[c]	8 (33.3)	4 (40.0)	4 (28.6)	
Duration of immune therapy at time of TPE onset > 180 days, n (%)	13 (54.2)	5 (50.0)	8 (57.1)	1.00[b]
Duration of immune therapy at time of TPE onset in days (median [IQR])	235 [0, 483]	164 [15, 399]	237 [0.00, 666]	0.66[d]

IQR, interquartile range; PERM, progressive encephalomyelitis with rigidity and myoclonus; *SD*, standard deviation; SPS, stiff person syndrome; SPSD, stiff person syndrome spectrum disorders; TPE, therapeutic plasma exchange.
[a]Two-tailed *t*-test.
[b]Fisher's Exact test.
[c]SPS-plus, Cerebellar ataxia, PERM (%).
[d]Kruskal–Wallis test.

Table 4. Literatuere review of SPSD patients treated with TPE.

Reference	Description	Anti-GAD65	IVIg	Rituximab	Other IS	TPE protocol	Outcome following TPE	Safety
Ehler *et al.*[14]	61-year-old male classic SPS	> 10,000 U/mL	N/A	N/A	Dexamethasone Azathioprine	5 sessions	Improvement	Not reported
Katoh *et al.*[15]	59-year-old female classic SPS	19,900 U/mL	Yes	Yes	No	N/A	Not specified Improvement attributed to rituximab	Not reported
Iwata *et al.*[16]	79-year-old female classic paraneoplastic SPS	56,400 U/mL	No	No	No	3 sessions	Improvement	Not reported
Solimena *et al.*[17]	49-year-old female classic SPS	Positive[a]	No	No	No	5 sessions	Improvement	Not reported
Chia *et al.*[18]	Middle-aged female classic SPS	> 187 U/L	Yes	No	No	3 sessions	No improvement	Not reported
Brashear and Phillips[19]	37-year-old female classic SPS	Positive[a]	No	No	No	5 sessions	Improvement	Not reported
Czempik *et al.*[20]	49-year-old female classic SPS	> 2000 U/mL	No	No	Methylprednisolone	5 sessions	Improvement	No complications
Nakamagoe *et al.*[21]	56-year-old male classic SPS	Negative[b]	No	No	Prednisolone	4 sessions	Improvement	Not reported
Barker *et al.*[22]	2 patients with classic SPS	Positive[a]	No	No	High-dose methylprednisolone	N/A	No improvement	Not reported
Hao *et al.*[23]	36-year-old female classic SPS	> 1:1000[c]	Yes	No	Prednisone Cyclophosphamide Mycophenolate mofetil	Chronic	Improvement	Vascular access infection with endocarditis
Shariatmadar and Noto[24]	36-year-old female classic SPS 49-year-old female classic SPS	Negative[b]	No	No	No	5 sessions	No improvement	No complications
De la Casa-Fages *et al.*[25]	2 patients, not otherwise specified	> 2000 U/mL[c]	No	No	Methylprednisolone Azathioprine	1×/week for 3 years	Improvement	No complications
Lehmann *et al.*[26]	1 female classic SPS	Positive[a]	No	No	No	N/A	Improvement	Not reported
Pagano *et al.*[13,d]	9 patients classic SPS	Positive (8) 3445 U/mL[e]	Yes	No	Cyclophosphamide (1)	5 sessions (7) 3 series of 5 sessions (2)	Improvement	Vascular access infection (1) Hypotension (1)
Georgieva and Parton[27]	45-year-old male SPS-plus	Positive[a]	Yes	No	Azathioprine	5 sessions every 4 months	Improvement	Not reported
Zdziarski[28]	39-year-old female classic SPS	> 1:20,000[c]	No	Yes	Mycophenolate mofetil	2 sessions	Improvement	Anemia

(Continued)

Table 4. (Continued)

Reference	Description	Anti-GAD65	IVIg	Rituximab	Other IS	TPE protocol	Outcome following TPE	Safety
Pham and Williams[29]	26-year-old female classic SPS 51-year-old female classic SPS	Positive[a]	Yes Yes	Yes No	No	4 sessions 5 sessions	Improvement	Hypotension (1) Citrate toxicity (1)
Albahra *et al.*[10]	9 females and 1 male classic SPS	325 IU/mL[e]	No (8) Yes (1)	No (8) Yes (1)	Mycophenolate mofetil (1)	5 sessions and chronic sessions (6)	Improvement	Not reported
Harding *et al.*[30]	50-year-old male classic SPS 45-year-old male classic SPS	Positive[a]	No	No	Prednisolone Azathioprine	5 sessions	No improvement	Not reported
Fogan[31]	55-year-old female classic SPS	Negative[b]	No	No	Prednisolone Azathioprine	6 sessions	Improvement	Not reported
Holmoy *et al.*[32]	67-year-old male classic SPS	1.57 units	No	No	No	5 sessions	No improvement	Lymph leakage and vascular access pain
Esplin *et al.*[33]	65-year-old male PERM	Positive,[a] titer 1:250	Yes	No	Tacrolimus	5 sessions	No improvement	Not reported
Cervantes *et al.*[34]	46-year-old male partial SPS	64 IU/mL	Yes	Yes	No	5 sessions	No improvement	Not reported
Sanchez *et al.*[35]	30-year-old female classic SPS	250 IU/mL	Yes	No	No	5 sessions	Improvement	Not reported
Hinson *et al.*[36]	68-year-old male classic SPS	$>$ 250 IU/L[c]	Yes	No	No	7 sessions	Improvement	Not reported
Grech *et al.*[37]	1 partial SPS 2 PERM 2 classic SPS	Negative[b]	Yes (4) No (1)	Yes (2) No (3)	Mycophenolate mofetil (1)	N/A	Improvement (4) No improvement (1)	Not reported
Jazebi *et al.*[38]	65-year-old male PERM	Negative[b]	Yes	No	No	5 sessions	Improvement	Not reported
Morise *et al.*[39]	72-year-old female PERM	74,000 U/mL serum 610 U/mL CSF	Yes	No	Prednisolone	7 sessions	Improvement	Not reported
Coles and Barker[9]	50-year-old female partial SPS	Negative[b]	No	No	Methylprednisolone Cyclophosphamide	2 sessions	Improvement	Not reported

IS, immunosuppressive medication; N/A, not available; PERM, progressive encephalomyelitis with rigidity and myoclonus; SPS, stiff person syndrome; SPSD, stiff person syndrome spectrum disorders; TPE, therapeutic plasma exchange.
[a]Positive anti-GAD test, exact value not available.
[b]Negative anti-GAD test, exact value not available.
[c]Value above the upper detection limit of the test.
[d]The patients of this study are also part of our study.
[e]Mean value.

respectively); this did not meet statistical significance ($p = 0.14$). We observed a similar trend when examining patients who required fewer symptomatic therapies after TPE *versus* those who did not, whereby the patients who required fewer medications after TPE were on average younger than those who did not (44 *versus* 50 years, respectively; $p = 0.30$) (Table 3).

When evaluating predictors of treatment response through multivariate analysis, there was no increased likelihood of overall treatment response when evaluating any of the independent factors of age [odds ratio (OR) 0.97, 95% confidence interval (CI) 0.91–1.0, $p = 0.18$], sex (OR 2.64, 95% CI 0.50–14.0, $p = 0.26$), SPS phenotype (OR 0.56, 95% CI 0.15–2.17, $p = 0.41$), or time on immunotherapy > 180 days (OR 1.62, 95% CI 0.44–5.98, $p = 0.47$). When evaluating for any predictors of reduced GABAergic medication requirements, there were also no observed association with any of the same independent variables of age (OR 0.97, 95% CI 0.91–1.03, $p = 0.35$), sex (OR 1.03, 95% CI 0.14–7.62, $p = 0.97$), SPS phenotype (OR 0.62, 95% CI 0.11–3.43, $p = 0.58$), or time on immunotherapy > 180 days (OR 1.31, 95% CI 0.26–6.65, $p = 0.75$).

Literature review

Review of the literature identified 57 additional cases of SPSD that were treated with TPE (Table 4). In reviewing the literature, there was a lack of standardized measures of improvement. The outcomes in most cases were descriptive. Forty-three (75%) patients were reported to have symptomatic improvement; 14 (25%) patients had no improvement. The reported degree and duration of clinical improvement was highly variable for each patient, ranging from mild to major improvement. In addition, the clinical benefits were temporary for each of these patients.

Discussion

The findings from this retrospective study of the largest cohort of SPSD patients treated with TPE suggest that TPE is safe, well-tolerated, and beneficial for many people with SPSD. A significant improvement in symptoms was observed in over half of our patients, with improvement in gait specifically noted in half of qualifying patients, and a small majority of patients demonstrating a sustained reduction in their use of symptomatic therapy after treatment of TPE. Moreover, there were a considerable number of patients who appeared to experience plateauing of their worsening clinical status with TPE; 81% of patients with no change in mRS, 36% reporting no improvement or worsening of symptoms, 67% demonstrating no improvement or worsening of gait. Our results coupled with those from the literature review suggest that the majority of patients experience some benefit from treatment with TPE. Overall, TPE may be a useful adjunctive therapy for patients with SPSD who are refractory to standard treatments (e.g. symptomatic and IVIg) in the appropriate clinical setting, whether as a rescue therapy for acute worsening or maintenance with worsening disability.

Two prior studies investigated the role of TPE in the management of SPSD. The first study evaluated only eight patients with the diagnosis of SPSD and showed partial or complete response in six of the patients.[9] The second study which demonstrated similar findings was done at JHH and evaluated only nine patients with only limited data assessed.[13] The mechanisms for therapeutic benefit with TPE are incompletely understood. Its efficacy in immune-mediated conditions may be ascribed to a reduction in circulating antibodies, immune complexes, and other immune-mediators, along with stimulation of lymphocytes that may enhance cytotoxic therapy.[40] In our study, as observed in prior studies, the response to TPE was variable, spanning profound improvement to no demonstrable effect[14,16–37,39]. The variability in treatment effect among the studies and case reports in the literature is in part due to the heterogeneity as to how the response to TPE has been evaluated, with a lack of uniform assessment of physical performance (e.g., rigidity, frequency of spasm, gait function, mRS). This variability makes it difficult to predict responses to treatment. In our study, we applied several standardized assessments of physical function to evaluate both patient's symptomatic response, quality of life, and overall level of function by assessing GABAergic medication requirements, mRS, and gait function, respectively. There was a small majority of patients who had a sustained decrease in their medication requirements 3 months after initial treatment with TPE, including in patients

who were already on immune therapy with IVIg and/or rituximab. This suggests that TPE could provide relief to patients with uncontrolled/poorly controlled symptoms despite being on multiple therapies, and may provide additional guidance on the use of TPE in chronic disease. The vast majority of patients did not demonstrate a worsening of their mRS 3 months after treatment, and this could also suggest that TPE can be used as a strategy to slow down clinical worsening in patients who might not respond to other therapies.

We also evaluated patients to assess if there were any predictive factors in treatment response, and did not find any that were statistically significant. The characteristic that was closest to demonstrating a benefit was age, as treatment responders were generally younger when evaluating both clinical response and medication requirements. This age-dependent predictor of treatment response has been shown in other chronic neurological diseases like progressive multiple sclerosis. However, we cannot posit whether this is a true signal in SPSD at this juncture due to our sample size. Further investigation of a larger sample of patients may provide clearer evidence on which patients are most likely to derive clinical benefit from treatment with TPE. While most of our clinical outcomes addressed the symptoms most typically identified in classic SPS and SPS-plus, of the three patients with CA, two reported improvement with TPE. The relationship between anti-GAD65 antibody levels and disease burden has been unclear, including if anti-GAD65 antibodies are actually pathogenic.[41,42] Notably, all three of our seronegative patients demonstrated clinical improvement with TPE, and in seropositive patients, anti-GAD65 levels remained elevated after treatment. This information could provide further support to the idea that therapeutic effect of TPE in SPSD is related to the removal of complement, cytokines, and other modulatory components of the immune system, rather than elimination of purported pathogenic antibodies.

The adverse effects observed were manageable and no permanent sequelae were noted. Previous studies have shown that TPE has an overall adverse event frequency of 4.75% and a calculated mortality between 1 and 2/10,000 per procedure. Common adverse effects (<10%) include symptomatic hypocalcemia (paresthesias, muscle cramps) and hypovolemia (hypotension, lightheadedness). Rare adverse effects (<1.5%) include alterations in acid-base homeostasis from citrate infused for anticoagulation, seizure, allergic reaction to albumin or catheter, catheter-associated infections, or thromboses. Repeated apheresis treatments with albumin replacement may result in depletion of clotting factors and immunoglobulins which may increase the risk of bleeding and infection.

This study has several limitations. It was a single-center retrospective analysis with small sample size and limited power to detect predictors of improvement or disease stabilization with TPE; nonetheless, it remains the largest descriptive assessment of TPE for SPSD to date. We did not have a control group based on the nature of the study, which impacts the generalizability of the findings. Another limitation is that many of these individuals were on multiple treatments, which makes it difficult to accurately separate out the full effectiveness of TPE. While not unique to this study, there is heterogeneity in the disorders treated, and reporting of clinical outcomes after TPE treatment was not consistent for all patients (e.g., particularly for TPE that was performed outside JHH). TPE is also typically performed at large, tertiary academic centers with a dedicated apheresis service and specialized medical staff. There was variability in the timing of TPE relative to symptom onset, and there is confounding by primary indication of treating acute exacerbations. In addition, TPE was used primarily in a treatment refractory group (35/39 patients were already being treated with concurrent immune therapy), which may skew the results toward a lack of treatment response and limits generalizability of overall use of TPE, but this treatment approach is consistent with standard of practice. Furthermore, most patients were treated with a new immune therapy after TPE, which could also have altered their overall disease course. Finally, the post-PLEX treatment follow-up was capped at 3 months based on suspected duration of treatment effect, and thus our understanding of longer-term treatment effects is unknown.

In conclusion, TPE appears safe and well-tolerated in the treatment of SPSD and should be considered for some patients, particularly in those who fail to respond to first- and

second-line therapies such as benzodiazepines or IVIg and rituximab.[1] The complications of TPE that were observed were manageable and without sequelae. Our findings suggest that there is a sustained improvement in the symptoms of stiffness and rigidity in a majority of patients and importantly clinical worsening was halted following acute TPE treatment in many. Further investigation is needed to identify which patients are the best candidates for TPE in the acute setting, as well as who should receive chronic treatment with outpatient TPE for maintenance therapy in SPSD.

Declarations

Ethics approval and consent to participate

This study was approved by the Johns Hopkins University Institutional Review Board under IRB00154798. Written informed consent for both participation and publication was obtained from participating patients, and the requirement for written consent was waived for select cases by the Institutional Review Board where it was deemed impractical to obtain.

Consent for publication

Not applicable.

Author contributions

Nicolas Mercure-Corriveau: Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

Shuvro Roy: Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

Chen Hu: Formal analysis; Writing – review & editing.

Elizabeth P. Crowe: Formal analysis; Writing – review & editing.

Xianming Zhu: Formal analysis; Writing – review & editing.

Danielle Obando: Data curation; Formal analysis; Writing – review & editing.

Eshan U. Patel: Formal analysis; Writing – review & editing.

Aaron A. R. Tobian: Formal analysis; Writing – review & editing.

Yujie Wang: Data curation; Formal analysis; Writing – review & editing.

Evan M. Bloch: Conceptualization; Formal analysis; Writing – original draft; Writing – review & editing.

Scott D. Newsome: Conceptualization; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

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Availability of data and materials

Anonymized data will be shared by the corresponding author upon reasonable request.

ORCID iDs

Nicolas Mercure-Corriveau https://orcid.org/0000-0002-1037-3594

Shuvro Roy https://orcid.org/0000-0002-3240-7441

Supplemental material

Supplemental material for this article is available online.

References

1. Dalakas MC, Fujii M, Li M, *et al.* The clinical spectrum of anti-GAD antibody-positive patients with stiff-person syndrome. *Neurology* 2000; 55: 1531–1535.
2. Newsome SD and Johnson T. Stiff person syndrome spectrum disorders; more than meets the eye. *J Neuroimmunol* 2022; 369: 577915.
3. Budhram A, Sechi E, Flanagan EP, *et al.* Clinical spectrum of high-titre GAD65 antibodies. *J Neurol Neurosurg Psychiatry* 2021; 92: 645–654.
4. Yi J and Dalakas MC. Long-term effectiveness of IVIg maintenance therapy in 36 patients with GAD antibody–positive stiff-person syndrome. *Neurol Neuroimmunol Neuroinflamm* 2022; 9: e200011.
5. Dalakas MC, Rakocevic G, Dambrosia JM, *et al.* A double-blind, placebo-controlled study of rituximab in patients with stiff person syndrome. *Ann Neurol* 2017; 82: 271–277.
6. Bhatti AB and Gazali ZA. Recent advances and review on treatment of stiff person syndrome in adults and pediatric patients. *Cureus* 2015; 7: e427.
7. Adams WS, Blahd WH and Bassett SH. A method of human plasmapheresis. *Proc Soc Exp Biol Med* 1952; 80: 377–379.
8. Padmanabhan A, Connelly-Smith L, Aqui N, *et al.* Guidelines on the use of therapeutic apheresis in clinical practice: evidence-based approach from the Writing Committee of the American Society for Apheresis – the eighth special issue. *J Clin Apher* 2019; 34: 171–354.
9. Coles A and Barker R. A case of stiff limb syndrome responsive to plasma exchange. *J Neurol Neurosurg Psychiatry* 2001; 70: 407–408.
10. Albahra S, Yates SG, Joseph D, *et al.* Role of plasma exchange in stiff person syndrome. *Transfus Apher Sci* 2019; 58: 310–312.
11. Ciccoto G, Blaya M and Kelley RE. Stiff person syndrome. *Neurol Clin* 2013; 31: 319–328.
12. Pittock SJ, Lucchinetti CF, Parisi JE, *et al.* Amphiphysin autoimmunity: Paraneoplastic accompaniments. *Ann Neurol* 2005; 58: 96–107.
13. Pagano MB, Murinson BB, Tobian AA, *et al.* Efficacy of therapeutic plasma exchange for treatment of stiff-person syndrome. *Transfusion* 2014; 54: 1851–1856.
14. Ehler E, Latta J, Mandysová P, *et al.* Stiff-person syndrome following tick-borne meningoencephalitis. *Acta Medica* 2011; 54: 170–174.
15. Katoh N, Matsuda M, Ishii W, *et al.* Successful treatment with rituximab in a patient with stiff-person syndrome complicated by dysthyroid ophthalmopathy. *Intern Med* 2010; 49: 237–241.
16. Iwata T, Inoue K, Mizuguchi S, *et al.* Thymectomy for paraneoplastic stiff-person syndrome associated with invasive thymoma. *J Thorac Cardiovasc Surg* 2006; 132: 196–197.
17. Solimena M, Vicari AM, Pozza G, *et al.* Plasmapheresis in the treatment of stiff-man syndrome. *N Engl J Med* 1989; 320: 1499.
18. Chia SY, Chua R, Tan EK, *et al.* Acute ataxia, Grave's disease and stiff person syndrome. *Mov Dis* 2007; 22: 1969–1971.
19. Brashear HR and Phillips LH 2nd. Autoantibodies to GABAergic neurons and response to plasmapheresis in stiff-man syndrome. *Neurology* 1991; 41: 1588–1592.
20. Czempik PF, Gawryluk J, Wiorek A, *et al.* Efficacity and safety of therapeutic plasma exchange in stiff person syndrome. *Open Med* 2021; 16: 526–531.
21. Nakamagoe K, Ohkoshi N, Hayashi A, *et al.* Marked clinical improvement by plasmapheresis in a patient with stiff-man syndrome: a case with a negative anti-GAD antibody. *Rinsho Shink* 1995; 35: 897–900.
22. Barker RA, Revesz T, Thom M, *et al.* Review of 23 patients affected by the stiff man syndrome: clinical subdivision into stiff trunk (man) syndrome, stiff limb syndrome, and progressive encephalomyelitis with rigidity. *J Neurol Neurosurg Psychiatry* 1998; 65: 633–640.
23. Hao W, Davis C, Hirsch IB, *et al.* Plasmapheresis and immunosuppression in stiff-man syndrome with type 1 diabetes: a 2-year study. *J Neurol* 1999; 246: 731–735.
24. Shariatmadar S and Noto TA. Plasma exchange in stiff-man syndrome. *Ther Apher* 2001; 5: 64–67.
25. De la Casa-Fages B, Anaya F, Gabriel-Ortemberg M, *et al.* Treatment of stiff-person syndrome with chronic plasmapheresis. *Mov Disord* 2012; 28: 396–397.
26. Lehmann HC, Hartung HP, Hetzel GR, *et al.* Plasma exchange in neuroimmunological disorders: part 2 – treatment of neuromuscular disorders. *Arch Neurol* 2006; 63: 1066–1071.
27. Georgieva Z and Parton M. Cerebellar ataxia and epilepsy with anti-GAD antibodies: treatment

with IVIG and plasmapheresis. *BMJ Case Rep* 2014; 2014: bcr2013202314.

28. Zdziarski P. A case of stiff person syndrome: immunomodulatory effect of benzodiazepines: successful rituximab and tizanidine therapy. *Medicine* 2015; 94: e954.
29. Pham HP and Williams LA. Therapeutic plasma exchange in two patients with stiff-person syndrome. *J Clin Apher* 2015; 31: 493–494.
30. Harding AE, Thompson PD, Kocen RS, *et al*. Plasma exchange and immunosuppression in the stiff man syndrome. *Lancet* 1989; 2: 915.
31. Fogan L. Progressive encephalomyelitis with rigidity responsive to plasmapheresis and immunosuppression. *Ann Neurol* 1996; 40: 451–453.
32. Holmøy T, Skorstad G, Røste LS, *et al*. Stiff person syndrome associated with lower motor neuron disease and infiltration of cytotoxic T cells in the spinal cord. *Clin Neurol Neurosurg* 2009; 111: 708–712.
33. Esplin NE, Stelzer JW, Legare TB, *et al*. Difficult to treat focal, stiff person syndrome of the left upper extremity. *Case Rep Neurol Med* 2017; 2017: 2580620.
34. Cervantes CE, Lee Lau H, Binazir TA, *et al*. Why it is not always anxiety: a tough diagnosis of stiff person syndrome. *Case Rep Neurol Med* 2017; 2017: 7431092.
35. Sanchez K, Ullah A, Waler AR, *et al*. Improving ambulation and minimizing disability with therapeutic plasma exchange in a stiff-person syndrome patient with recurrent falls. *Cureus* 2019; 11: e6209.
36. Hinson SR, Lopez-Chiriboga AS, Bower JH, *et al*. Glycine receptor modulating antibody predicting treatable stiff-person spectrum disorders. *Neurol Neuroimmunol Neuroinflamm* 2018; 5: e438.
37. Grech N, Galizia JPC and Pace A. Progressive encephalomyelitis with rigidity and myoclonus (PERM). *Pract Neurol* 2022; 22: 48–50.
38. Jazebi N, Rodrigo S, Gogia B, *et al*. Anti-glutamic acid decarboxylase (GAD) positive cerebellar Ataxia with transitioning to progressive encephalomyelitis with rigidity and myoclonus (PERM), responsive to immunotherapy: a case report and review of literature. *J Neuroimmunol* 2019; 332: 135–137.
39. Morise S, Nakamura M, Morita JI, *et al*. Thymoma-associated progressive encephalomyelitis with rigidity and myoclonus (PERM) with myasthenia gravis. *Intern Med* 2017; 56: 1733–1737.
40. McKeon A. Stiff-man syndrome and variants. *Arch Neurol* 2012; 69: 230–238.
41. Baizabal-Carvallo JF and Jankovic J. Stiff-person syndrome: insights into a complex autoimmune disorder. *J Neurol Neurosurg Psychiatry* 2015; 86: 840–848.
42. Rakocevic G, Raju R and Dalakas MC. Anti-glutamic acid decarboxylase antibodies in the serum and cerebrospinal fluid of patients with stiff-person syndrome: correlation with clinical severity. *Arch Neurol* 2004; 61: 902–904.