Efficacy of therapeutic plasma exchange for treatment of stiff-person syndrome

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BACKGROUND: The efficacy of therapeutic plasma exchange (TPE) in stiff-person syndrome (SPS) is unclear.

STUDY DESIGN AND METHODS: A retrospective analysis of patients diagnosed with SPS who underwent TPE and a systematic literature review were conducted.

RESULTS: Nine patients with the presumptive diagnosis of SPS who underwent TPE were identified. The mean age was 55 years (range, 34-72 years) and 78% (n = 7) were female. Anti-GAD65 was present in 89% (n = 8) of the patients (range, 1.9-40,000 U/mL), and 33% (n = 3) had a history of diabetes. Forty-four percent (n = 4) of patients had previously received immunosuppressive medication and 67% (n = 6) received intravenous immune globulin. The main indication for TPE was worsening of symptoms despite treatment with first-line therapy. Seventy-eight percent of the patients (n = 7) had five TPE procedures. Seventy-eight percent (n = 7) of patients demonstrated at least minimal clinical improvement and 56% (n = 5) had a significant response. Most of the patients who demonstrated a significant response to treatment improved and their symptoms stabilized. Two patients (22%) developed adverse events, including catheter-associated infection and transient hypotension. Eighteen publications were found from the literature review, which resulted in a total of 26 patients diagnosed with SPS. Forty-two percent (n = 11) of patients had a significant symptomatic improvement after TPE treatment, and two patients (8%) developed adverse events.

CONCLUSION: TPE may benefit patients with SPS who are not responsive to first-line therapy, and it is well tolerated.

Stiff-person syndrome (SPS) is a rare and disabling disorder characterized by rigidity and painful spasms that mainly compromise the axial musculature.[1] Typically, SPS affects middle-age individuals, females being affected more frequently than males.[2] The diagnosis is based on clinical, electromyography, and laboratory findings. Current diagnostic clinical criteria include the presence of progressive stiffness, cocontraction of agonist and antagonist muscles that can be observed clinically and confirmed by electromyography, sudden episodic spasms precipitated by various stimuli, and the absence of other neurologic disorders accounting for the symptoms.[3]

A history of autoimmune disorders is frequently observed in SPS patients, including diabetes, Graves' disease, hypothyroidism, pernicious anemia, and vitiligo, and approximately 85% of the patients demonstrate the presence of glutamic acid decarboxylase antibodies (anti-GAD65).[4,5] These antibodies are also found in patients with diabetes mellitus with different epitope specificities and lower titers.[2] Although antibody titers do not correlate with disease activity, SPS patients typically have very high antibody levels.[6] Amphiphysin antibodies are found in approximately 10% of SPS patients and are often associated with cancer, most commonly breast cancer.[7]

ABBREVIATIONS: GABA = gamma-aminobutyric acid; JHH = Johns Hopkins Hospital; SPS = stiff-person syndrome; TPE = therapeutic plasma exchange.

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The pathophysiology of the disease and the role of autoantibodies are not fully understood. Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter and its absence can result in excessive or sustained muscular excitability. GAD65 is the rate-limiting enzyme for the synthesis of GABA and is concentrated in presynaptic terminals.[5] Evidence of the pathophysiologic role of anti-GAD65 in the disease is supported by the finding that when anti-GAD65 from SPS patients was given to rats, an increased excitability of the spinal cord was observed.[8] In vitro experiments have demonstrated that in the presence of anti-GAD65, GABA synthesis is decreased, but it is not certain whether the same mechanism occurs in vivo.[9] Amphiphysin is a protein responsible for endocytosis, but its pathophysiologic role in the disease is less clear.[5] GAD65 and amphiphysin are intracellular presynaptic proteins, and their epitopes can be exposed to antibodies after synaptic vesicle fusion and reuptake.[10]

First-line therapy for SPS patients includes the use of GABAergic agonists including benzodiazepines and baclofen for symptomatic management. Intravenous immune globulin (IVIG) has been proven in a randomized control trial to be effective in improving symptoms.[11] Immunosuppressive medication alone or in combination with therapeutic plasma exchange (TPE) has been used in refractory cases but its effectiveness is still uncertain. No randomized control trials have been performed to demonstrate the efficacy of TPE, and only a few case reports have been published with positive[12-25] and negative outcomes.[17,22,26-29] Taking into consideration the unclear role of anti-GAD65 and the lack of treatment consensus when first-line therapy fails, these contradictory outcomes after apheresis may imply that SPS is a heterogeneous disease.

The aim of our study was to review our center's experience of patients with a presumptive diagnosis of SPS undergoing TPE and evaluate their response to treatment, with special attention to the presence of adverse effects. All currently published cases of SPS in which TPE was performed were reviewed, and the results of this analysis are also reported here.

MATERIALS AND METHODS

Case series

The study was approved by the Johns Hopkins Institutional Review Board. A search for patients with the presumptive diagnosis of SPS who received TPE was performed in the Johns Hopkins Hospital (JHH) Hemapheresis and Transfusion Support database from 1996 to 2012. After the patients were identified, a retrospective review of electronic and paper medical records was performed to gather information about sex, age, comorbidities, previous treatments, clinical response to treatment, and results of anti-GAD65 and amphiphysin antibody testing. Clinical materials were reviewed by a neurologist experienced in the diagnosis of SPS (BBM), to establish a "final neurologic diagnosis."

Literature review

A systematic search of the literature was performed using Medline to identify reports of randomized and observational studies of patients with the diagnosis of SPS who underwent TPE. The search terms in different combinations included "stiff person syndrome," "plasmapheresis," "therapeutic plasma exchange," and "treatment." The search was limited to articles published in English. All observational studies that provided relevant data, including papers, abstracts, correspondence, case series, or case reports, were included.

Clinical improvement score

To evaluate the clinical improvement to TPE treatment, a numeric (1 to 3) severity score was developed based on the descriptive and global assessment that the neurologists used to describe the response to treatment. A clinical response Grade 1 was given when the neurologist caring for the patient described that the patient did not have any improvement in symptoms after receiving TPE. A clinical response Grade 2 was given when the patient did have some, partial, or minimal improvement of symptoms that did not result in significant change in daily activities, but resulted in an improvement when compared to the response to standard therapy. A clinical response Grade 3 was given when the clinical improvement was significant enough to impact the daily activities of the patient, including improvement in speech, balance, overall rigidity, and decreasing frequency of spasms. This score was used to measure clinical response in patients found at Johns Hopkins and in patients found in the literature review.

Statistical analysis

Association between treatment response and clinical variables was estimated using both pairwise correlation and logistic regression. Clinical variables included number of TPEs, history of immunosuppressive medication, IVIG, presence of anti-GAD65, diabetes, autoimmune disease, and cancer. All estimations were conducted in computer software (STATA 10, StataCorp, College Station, TX).

RESULTS

JHH patients and TPE description

Nine patients with an initial diagnosis of SPS received TPE at JHH between 1996 and 2012. Patients' characteristics

TABLE 1. Description of patients with SPS who received TPE at JHH

Patient	Sex, age (years)	Anti-GAD65* (U/mL)	Final diagnosis	Comorbidities	Cancer
1	Male, 45	239.7	SPS-R†	Diabetes	No
2	Female, 65	86.6	SPS-X‡	MGUS‖, diabetes	No
3	Female, 48	>30	SPS-R	Hepatitis C	No
4	Female, 61	1.9	SPS-A§	None	No
5	Male, 72	2	West Nile encephalitis	West Nile encephalitis	Colon
6	Female, 54	<0.1	Other	Hypothyroidism, MGUS	Breast
7	Female, 34	>30	SPS-R	Diabetes Type 1	No
8	Female, 50	>30	SPS-X	IgA deficiency	No
9	Female, 70	24,200	SPS-X	Psoriasis, hypertension	Melanoma

* Anti-GAD65 negative: < or = 1.0 U/mL.
† SPS-R = SPS associated with rigidity and muscle spasms.
‡ SPS-X = SPS associated with ataxia and speech dysfunction.
§ SPS-A = SPS associated with amphiphysin antibodies.
‖ MGUS = monoclonal gammopathy of undetermined significance.

are described in Table 1. The mean age was 55 years (range, 34-72 years) and 78% (n = 7) were female. Anti-GAD65 was present in 89% (n = 8) of the patients; two of these patients had very low levels of antibodies detected. A minority of patients, 33% (n = 3), had a history of diabetes, and 33% (n = 3) had a history of cancer. One patient demonstrated amphiphysin antibodies; however, no malignancy was identified despite 5 years of follow-up.

TPE was performed using an apheresis system (COBE Spectra, Terumo BCT, Lakewood, CO). All of the patients underwent TPE through a central line and received 110% replacement fluid with 50% normal saline and 50% albumin 5%, and ACD was used as the anticoagulant.

The main indication for TPE was worsening of symptoms despite treatment with first-line therapy in seven of the nine patients, of which four had previously received IVIG (Patients 4, 5, 7, and 9), one had received treatment with lorazepam (Patient 6), one was not eligible for IVIG due to IgA deficiency (Patient 8), and one had received immunosuppressive therapy with a combination of steroids and cyclophosphamide (Patient 2). Of the remaining two patients, one patient underwent TPE for suspected paraneoplastic syndrome, which was later diagnosed as SPS, and one patient received TPE in combination with baclofen as part of the initial treatment. Seven patients received one series of five TPE treatments, and two patients received two and three series of five TPE treatments, respectively.

Final neurologic diagnoses were established for all nine patients (Table 1). Three patients demonstrated clinical features consistent with the primary form of SPS associated with rigidity and muscle spasms, here designated SPS-R. Three patients had a clinical picture consistent with the ataxic form of SPS, displaying prominent ataxia and speech dysfunction, here designated SPS-X. One patient had SPS associated with amphiphysin antibodies, SPS-A. One patient was later diagnosed as having a centrally mediated disorder with central planning impairment, in the context of surviving breast cancer. One patient's clinical manifestations were interpreted as SPS-like secondary to West Nile virus infection.

Response to treatment and adverse events

The response to treatment expressed by the clinical improvement score is shown in Table 2. Of the patients who demonstrated mild improvement, Patient 1 underwent placement of baclofen intrathecal pump and the symptoms remained stable after a follow-up of 11 years. Patient 4 had slow progression of symptoms and was started on treatment with mycophenolate mofetil.

Fifty-six percent (n = 5) of patients had a significant response (score 3) that resulted in substantial impact on communication skills and mobility. Among these five patients, TPE seemed to improve symptoms and stabilize disease progression in four of them. Patient 3 continued treatment with baclofen, diazepam, and monthly IVIG with stable symptoms after 3 years of follow-up. Patient 6, who was originally treated as SPS and later was confirmed to have a paraneoplastic centrally mediated disorder with central planning impairment, had good response to TPE and continued diazepam and baclofen with 4 years of follow-up. Evidence suggests that there is a role for TPE in paraneoplastic syndromes, which could explain the good response to TPE in this patient.[30] Patient 7 continued receiving IVIG every 4 to 6 weeks to maintain the improvement achieved by TPE during 1 year of follow-up, and Patient 9 received two cycles of five TPE procedures in a 3-month period and continued maintenance treatment with baclofen and diazepam with symptoms remaining stable after 3 months of follow-up. Patient 8 had an initial significant response to TPE, but subsequently had progression of disease. This last patient received three cycles of five TPE procedures in a 12-month period; with each TPE cycle the symptoms improved, but this improvement was temporary and the patient continued developing neurologic deterioration despite receiving mycophenolate mofetil and rituximab infusions.

TABLE 2. Treatment and outcome for patients with SPS who received TPE at JHH*

Patient	Number of TPE procedures	IVIG	Immunosuppressive therapy	Outcome	Clinical improvement score
1	5	No	No	Improved rigidity	2
2	5	Yes†	Yes‡	No benefits	1
3	5	Yes§	No	Improved speech, diplopia, dysmetria, and strength	3
4	5	Yes‡	Yes§	Improved spasticity	2
5	5	Yes†‡	Yes†	No benefits	1
6	5	No	No	Improved ambulation, coordination, and speech	3
7	5	Yes‡§	No	Improved mobility, rigidity, and tremor	3
8	5 × 3	No	Yes§	Improved ambulation and rigidity	3
9	5 × 2	Yes‡	No	Improved balance and speech	3

* Patient 2 received cyclophosphamide and prednisone before TPE treatment. Patient 4 received mycophenolate mofetil after TPE. Patient 5 received methylprednisolone during TPE, and Patient 8 received mycophenolate mofetil and rituximab after TPE treatment.
† During TPE.
‡ Before TPE.
§ After TPE.

TABLE 3. Description of patients with SPS who received TPE found in the literature

Patients	Number (%)	Information available
Female	15 (63)	24
Anti-GAD65	14 (61)	23
Diabetes	7 (29)	24
Autoimmunity*	6 (25)	24
Cancer†	4 (17)	24
Anti-amphiphysin	1 (100)	1
IVIG	6 (23)	26
Immunosuppressive medication	16 (62)	26

* Hashimoto, Graves (2), vitiligo, pernicius anemia, rheumatoid arthritis.
† Thymoma, breast, lung, mesopharyngeal carcinoma.

Two patients developed adverse events related to apheresis. Patient 1 experienced transient hypotension during a TPE procedure that resolved by pausing the procedure and administering normal saline and albumin boluses; Patient 8 had a catheter-associated infection that resolved after antibiotic treatment. There were no deaths associated with TPE treatment.

Literature review

Eighteen publications were found including 13 single case reports,[12-19,23,24,26,27,29] two case series,[22,28] one abstract,[21] one brief report,[20] and one correspondence.[25] A total of 26 patients were described, of which 24 patients received TPE and two patients received double-filtration plasmapheresis.[19,21] Patients' characteristics are described in Table 3. Description of the TPE procedure was not available for most of the patients. Fourteen patients received between three and five TPE treatments,[14,17,19,21-23,25-27,29] seven patients received between six and 11,[12,15-17,20,22,24] and one patient received approximately 64[18] TPE treatments in a 6-month period. Before starting TPE, most of the patients had received different combination treatments with baclofen, benzodiazepines, IVIG, and immunosuppressive medication.

Using the same clinical improvement score that was used to classify the patients at JHH, it was found that 38% (n = 10) of the patients had no response to treatment;[17,22,26-29] 19% (n = 5) had minimal, partial, or sporadic improvement;[13,17,22,24] and 42% (n = 11) had a significant symptomatic improvement after TPE treatment.[12,14-16,18-23,25] Two patients (22.2%) developed adverse events, including one patient with lymphoid leakage and pain at the catheter site[26] and one patient with line infection.[18] Two patients presented with technical problems during the third TPE treatment for which details were not given, but further TPE was not pursued.[22] No deaths associated with TPE were reported. Most of the reports involving 73% of the patients did not specify whether the patient did or did not have adverse events.

Predictors of treatment response

Pairwise correlation and regression analyses were conducted on the combination of nine patients from our clinic and 26 patients from the literature review. Both pairwise correlations and logistic regression showed no significant association between treatment response and any clinical variable at the 5% level (Table 4).

DISCUSSION

TPE has long been considered for treatment of patients with SPS who are not responsive to first-line therapy. Nine patients from JHH and 26 patients from the literature with the presumptive diagnosis of SPS who underwent TPE were reviewed. A distribution-of-stiffness score and heightened-sensitivity scale have been previously used to assess response to treatment.[11] In this observational retrospective review, it was not possible to use this

TABLE 4. Correlation between clinical variables and response to TPE treatment

Clinical variables	Correlation	p value
Anti-GAD	−0.375	0.080
Diabetes	0.065	0.764
Autoimmune disease	0.000	1.000
Cancer	0.316	0.132
Number of TPE	0.230	0.300
IVIG	0.058	0.770
Immunosuppressive medication	0.188	0.350

standardized score and a new score based on a more global, nonspecific description of improvement was developed. Using this score, 78% (n = 7) of the patients at JHH and 61% (n = 16) of the patients found in the literature had a positive response to TPE with at least minimal improvement in clinical symptoms. Most of the patients who demonstrated significant response to treatment achieved improvement of their symptoms and stabilization of the disease.

None of the clinical variables analyzed in this study were significant to predict a positive response to TPE. It is important to highlight the heterogeneity of this small group of patients who have varied clinical characteristics and different antibody levels. Murinson and coworkers[6] demonstrated that antibody levels did not correlate with age or disease duration, but high levels of antibodies correlated with the diagnosis of SPS, whereas low levels did not. Furthermore, patients with low levels of GAD65 antibodies related to diabetes who present with stiffness can be mistakenly diagnosed as SPS. Dalakas and coworkers[11] were able to show an excellent response to IVIG treatment in a homogenous and strictly selected population of SPS patients with high GAD65 antibodies, but it is not known if patients with low GAD65 antibodies would have the same response. In our center, those patients with antibody levels greater than 30 U/mL were likely to have a response to TPE therapy (five of six patients in this category showed minimal or better improvement, four of six showed marked improvement).

Therapeutic apheresis is usually well tolerated, with a described overall adverse event frequency of 4.75%[31] and a calculated mortality between 1 and 2 per 10,000 TPE procedures.[32] Adverse events were present in two patients (22%) from our center experience and two patients (8%) from the literature review. From a total of 60 procedures performed at JHH, only two (3.3%) procedures resulted in adverse events. Overall, TPE for SPS was found to be safe and caused no harm.

Based on our analysis of patients treated at JHH and those found in the literature, we conclude that most of the patients had at least minimal clinical improvement after TPE treatment when first-line therapy had failed and that TPE was very well tolerated. This study has several limitations including its retrospective nature, the limited inclusion of patients that were referred to the transfusion medicine service for TPE, and the absence of a control group. Further studies are needed to determine which patients are more likely to have a good response to TPE treatment.

CONFLICT OF INTEREST

The authors report no conflicts of interest or funding sources.

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