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ORIGINAL COMMUNICATION

Immunotherapy with subcutaneous immunoglobulin or plasmapheresis in patients with postural orthostatic tachycardia syndrome (POTS)

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Abstract

Background Postural orthostatic tachycardia syndrome (POTS), one of the most common autonomic disorders, is associated with significant morbidity and functional impairment. Although several possible etiologies have been proposed, autoimmunity has emerged as one of the leading causes with various specific and non-specific antibodies identified in patients with POTS. Treatment with intravenous immunoglobulin has been previously described. We present a case series of patients with severe POTS refractory to the standard pharmacologic and non-pharmacologic therapies treated with immunotherapy consisting of either subcutaneous immunoglobulin (SCIG) therapy or plasmapheresis (PLEX) and report their treatment outcomes.

Methods Clinical history of 7 patients with POTS who were treated with SCIG or PLEX was reviewed. Response to treatment was assessed using COMPASS 31 and functional ability scale (FAS), completed by patients retrospectively, pre- and 3–12 months post-treatment with SCIG or PLEX.

Results All patients improved following SCIG or PLEX with an average 50% reduction in COMPASS 31 score and 217% increase in FAS scores. Six out of seven patients were able to reduce or discontinue oral medications for POTS, and five patients were able to return to work or school. Four patients had skin biopsy or quantitative sudomotor axon reflex test (QSART)-proven small fiber neuropathy, and five had various positive antibodies at low titers.

Conclusion Patients with severe, treatment-refractory POTS experienced significant functional improvement with reduction in the autonomic symptoms following immunotherapy with SCIG or PLEX. Randomized controlled trials of SCIG and/or PLEX are needed to determine the efficacy and safety of these long-term therapies in patients with POTS.

Keywords Postural orthostatic tachycardia syndrome · Immunotherapy · Subcutaneous immunoglobulin therapy · Plasmapheresis · Autonomic disorders

Introduction

Postural orthostatic tachycardia syndrome (POTS), one of the most common autonomic disorders, may be associated with significant morbidity and functional impairment [1]. POTS is defined by an increase in heart rate of at least 30 beats per minute in adults and at least 40 bpm in adolescents or children within 10 min of standing or a tilt table test and is associated with symptoms of orthostatic intolerance [1]. The most common symptoms and signs of POTS are lightheadedness/dizziness, postural tachycardia, presyncope, headache, fatigue, and difficulty concentrating [2]. Other symptoms include gastrointestinal symptoms, shortness of breath, chest pain, blurred vision, myalgias, cold extremities, and muscle weakness [2, 3]. Over the past decade, autoimmunity has emerged as one of the leading etiologies of POTS [4, 5].

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Case series of successful treatment of POTS with intravenous immunoglobulin (IVIG) and isolated case reports of patients treated with plasmapheresis have been described in the literature. [5–9] In this case series, we report 7 patients with POTS who were successfully treated with subcutaneous immunoglobulin (SCIG) or plasmapheresis (PLEX). To our knowledge, the use of SCIG for treatment of POTS has not been previously reported.

Methods

Patients were recruited from Dysautonomia Clinic (SB), Center for Multisystem Disease (JS), and an online support group between 2019 and 2020. Inclusion criteria were 1. A diagnosis of POTS on a tilt table test or 10-min stand test associated with chronic symptoms of orthostatic intolerance 2. Treatment with SCIG or PLEX for at least 3 months.

Exclusion criteria were 1. Confirmed autoimmune disorders such as Sjogren's syndrome, antiphospholipid syndrome, celiac disease, systemic lupus erythematosus, rheumatoid arthritis, scleroderma, Chron's disease, ulcerative colitis, and active Lyme's disease. 2. Other autonomic disorders, such as orthostatic hypotension, orthostatic intolerance, neurocardiogenic syncope, pure autonomic failure, multiple system atrophy, autoimmune autonomic ganglionopathy, autoimmune autonomic neuropathy and orthostatic hypotension secondary to Parkinson's disease or diabetes. 3. Any immune deficiency disorders that may require treatment with immunoglobulin. Patients were allowed to have the following conditions comorbid with POTS: Ehlers–Danlos syndrome (EDS), mast cell activation syndrome (MCAS), small fiber neuropathy (SFN), and Hashimoto's thyroiditis.

Patients who qualified for the study completed questionnaires, and data were extracted on demographics, diagnoses, associated markers of autoimmunity, symptoms, disease duration, brand of immunoglobulin therapy, maintenance dose, Composite Autonomic Symptom Score 31 (COMPASS 31) and Functional Ability Scale (FAS) pre- and 3–12 months post- immunotherapy initiation, prior treatment with intravenous immunoglobulin therapy, and discontinued medications after improvement with SCIG or PLEX. COMPASS 31 and FAS questionnaires were completed by the patients retrospectively. COMPASS 31 is a validated questionnaire that assesses the autonomic symptom burden. All patients were also assessed using an overall FAS which is similar to the chronic fatigue syndrome wellness score, a validated single item scale that has been shown to correlate with other self-rating instruments [10].

The study was approved by the University of Central Florida Institutional Review Board. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Out of 7 patients, (all females, age range 28–57 years), who had POTS confirmed on a tilt table test, 5 received SCIG and 2 received PLEX. Four patients had SFN confirmed by QSART or a skin biopsy; four patients had hypermobile EDS, two patients had positive nicotinic ganglionic acetylcholine receptor antibodies at low titers, and one patient had elevated adrenergic, muscarinic, angiotensin II type I and endothelin I receptor antibodies as part of the autoimmune panel performed by CellTrend GmbH (Luckenwalde, Germany) (Table 1). Only 2 of 7 patients had no identifiable antibodies assessed by a complete serum autoimmune panel. All serum antibodies were obtained prior to treatment with immunotherapy, and all 7 patients had severe and disabling POTS despite being treated with various pharmacologic and non-pharmacologic therapies prior to initiation of SCIG or PLEX.

Three to nine months after initiation of SCIG, all five patients had reduced COMPASS 31 scores by 8–74% and increased FAS scores by 80–300% compared to the pre-treatment scores (Table 1, Fig. 1). The average improvement in COMPASS 31 scores was 50%, and the average improvement in FAS scores was 217% for all study participants. One patient had a minimal reduction in the COMPASS 31 score, but a significant increase in the FAS score, which suggests that overall functioning may not have been fully captured by the COMPASS 31 score in that specific patient (Fig. 1). Six patients were able to either discontinue or reduce oral medications for POTS. Five patients had FAS scores greater than 80% indicating that they felt ready to return to work or attend school part-time or with modifications. Three patients reported feeling ready to return to work or school full-time. Based on the FAS scores, all patients were no longer bedbound after treatment with SCIG or PLEX. The most common SCIG brand received was Hizentra, with one patient receiving Hyqvia. Patients included in this cohort did not report any significant side effects to SCIG or PLEX. Patients treated with PLEX were able to reduce the frequency of treatments with one patient reducing to a maintenance dose of one treatment every 2 weeks and another patient continued PLEX once per month after addition of IVIG. There were no incidents of aseptic meningitis, thromboembolic events, or other serious adverse events in this case series.

Discussion

POTS commonly affects young, previously healthy women at the prime of their life [2]. Most POTS patients experience a chronic course of illness with periods of

Table 1 Clinical features and treatment outcomes in patients treated with SCIG or PLEX

N (age sex)	Diagnoses	Duration (years)	Positive antibodies	Symptoms	Meds prior to treatment	SCIG/PLEX administered	COMPASS 31 pre/post SCIG/PLEX	FAS pre/post SCIG/PLEX	Discontinued meds after SCIG/PLEX	COMPASS-31 % change	FAS % change
1 (28F)	POTS, MCAS, hEDS	3	g-AchR 0.05 nm/mol	Presyncope, dizziness, blurry vision, imbalance, generalized weakness, pupil abnormalities	Midodrine, pyridostigmine, fludrocortisone, metoprolol, fluoxetine, ivabradine, IV saline	Hyqvia 1.3 mg/kg monthly	45/17	40/90	All except ivabradine and IV saline	62	125
2 (30F)	POTS, SFN	3	AR1 81.5 AR2 66.0 M1 13.9; M2 65.3; M3 8.0; M4 13.2 AT1R 60.1 ETAR 63.1	Syncope, orthostatic intolerance, chest pain, palpitations, dyspnea, migraines, fatigue, nausea, constipation, diarrhea, rash, flushing, cognitive impairment, weakness, lower extremity pain	Metoprolol, midodrine	Hizentra 0.4 mg/kg monthly	50/16	20/80	None	68	300
3 (30F)	POTS, Raynaud's	20	g-AchR 0.19 nmol/L	Syncope, gastroparesis, numbness in extremities, temperature dysregulation, reduced touch sensation, lower extremity pain	Midodrine, paroxetine	Hizentra 0.8 mg/kg monthly	52/26	50/100	Midodrine	50	100
4 (57F)	POTS MCAS, hEDS	15	SCL-70 positive	Exertional intolerance, post exertional malaise, symptoms of hyper-POTS	Beta blocker	Hizentra 1.9 mg/kg monthly	25/23	30/80	Beta blocker, replaced with clonidine	8	166

Table 1 (continued)

N (age sex)	Diagnoses	Duration (years)	Positive antibodies	Symptoms	Meds prior to treatment	SCIG/PLEX administered	COMPASS 31 pre/post SCIG/PLEX	FAS pre/post SCIG/PLEX	Discontinued meds after SCIG/PLEX	COMPASS-31 % change	FAS % change
5 (32F)	POTS, SFN, Hashimoto's thyroiditis, asthma	15	ANA 1:160	Palpitations, tremors, generalized weakness, numbness	Metoprolol, IVIG	Hizentra 1.2 mg/kg monthly	31/8	50/90	IVIG	74	80
6 (33F)	POTS, SFN, hEDS, MCAS	4	None	Orthostatic intolerance, postural tachycardia and hypertension, dizziness, nausea, constipation, extremity pain, fatigue, generalized weakness, low grade fevers, poor appetite, muscle cramps	Pindolol, pyridostigmine, desmopressin,	2×weekly PLEX (every 3–4 days), after adding IVIG for 4 months was able to continue PLEX once per month	55/21	10/70	Pain meds including opioids, and biologic DMARD (cosentyx)	63	600
7 (33F)	POTS, hEDS, IIH, SFN, MCAS	17	None	Syncope, extremity pain, headache, tachycardia, dyspnea, chest pain, cognitive dysfunction, fatigue, generalized weakness, gastroparesis	Midodrine, propranolol, fludrocortisone	3×weekly every 6 weeks for 6 months, then 1×every 2 weeks	61/47	20/50	Fludrocortisone	22	150

SFN small fiber neuropathy, *POTS* postural orthostatic tachycardia syndrome, *hEDS* hypermobile Ehlers–Danlos syndrome, *MCAS* mast cell activation syndrome, *IIH* idiopathic intracranial hypertension, *g-AchR* ganglionic acetylcholine receptor antibody, *SCL* scleroderma antibody, *ANA* antinuclear antibody, *AR1/AR2* alpha-1/2 adrenergic receptor auto-antibody, *M1-4* muscarinic cholinergic receptor auto-antibody, *ETAR* endothelin-receptor-A IgG auto-antibody, *ATIR* angiotensin-II-receptor-1 IgG autoantibody, *FAS* functional ability scale

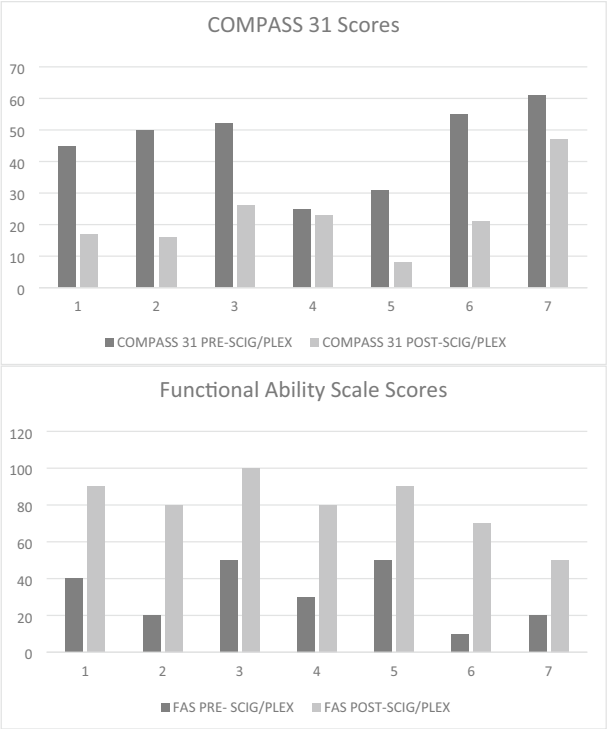

Fig. 1 Pre- and post-treatment COMPASS 31 and functional ability scale (FAS) scores in patients treated with SCIG or PLEX

improvement and exacerbation. Standard pharmacotherapy and non-pharmacologic measures may be suboptimal, and more than half of people with POTS are unemployed or unable to attend school [11]. The functional impairment from POTS has been compared to the disability seen in patients with congestive heart failure or chronic obstructive pulmonary disease [11]. In a large online study, 29% of POTS patients reported a slight improvement in their symptoms since disease onset and 13% reported a significant improvement [2]. One third of these patients reported that the improvement was attributed to medication [2]. The majority (58%) of patients, however, either reported no change or worsening of symptoms compared to when their symptoms began [2]. Better treatment strategies are critically needed to alleviate the functional impairment and reduce the disability burden in this patient population.

There is increasing evidence that autoimmunity is one of the underlying mechanism of POTS, with positive autoimmune markers and co-morbid autoimmune disorders being more prevalent in patients than in the general population [2, 12]. Specific autoantibodies to ganglionic acetylcholine receptor and G-protein coupled receptors, critical to the function of the autonomic nervous system, have been detected in patients with POTS, including ganglionic N-type and P/Q type acetylcholine receptor antibodies, alpha 1, beta 1 and beta 2 adrenergic antibodies, muscarinic M2 and M4 antibodies, angiotensin II type 1 receptor antibodies and opioid-like 1 receptor antibodies [4, 5, 13]. In the first animal model of POTS, Li et al. immunized rabbits with peptides from the alpha 1-adrenergic receptor and beta1-adrenergic receptor leading to these animals developing an enhanced heart response to isoproterenol and an attenuated pressor response to phenylephrine, a phenotype similar to POTS [14]. Li et al. also demonstrated the reversal of altered heart rate and blood pressure response with antibody-neutralizing peptides, which further supports an autoimmune etiology [14]. In our study, 5 of 7 patients had various positive antibodies at low titers on serum testing prior to treatment, and while the role and relevance of these antibodies in patients with POTS are unknown, the presence of these antibodies in the context of clinical picture of chronic and disabling symptoms, in conjunction with a favorable response to immunotherapy, raises a possibility of the autoimmune basis.

IVIG may be effective in treatment-refractory patients with POTS. Schofield et al. previously reported an improvement in FAS and COMPASS 31 scores in 84.5% of patients treated with IVIG [7]. There were no serious adverse events reported, and the pre-treatment medication regimen was modified specific to the most common reactions seen in this patient population to further alleviate IVIG-related side effects [15]. Most patients were able to return to work or school after being nearly bedridden prior to initiating treatment [7]. Although effective, IVIG is expensive and requires intravenous access as well as access to nursing care for administration. In contrast, SCIG does not involve intravenous access and is self-administered; it is also less expensive than IVIG and is often better tolerated with less side effects.

PLEX uses immunoadsorption to remove circulating antibodies and may be less expensive than IVIG. It may present an alternative treatment option when IVIG is denied by health insurance, is ineffective, or not well tolerated. In our case series, two patients reported significant clinical improvement after PLEX, although one patient reported further improvement with the addition of IVIG. Two patients treated with PLEX have been previously reported in the literature, which, included a patient with POTS following human papillomavirus vaccination whose symptoms significantly improved after plasmapheresis and prednisone [16]. Another case report described a patient with POTS following an episode of shingles who significantly improved after PLEX; attempts at discontinuation resulted in return of symptoms prompting the patient to remain on maintenance therapy [8].

Small fiber neuropathy (SFN) is one of the most common comorbidities in POTS occurring in at least 50% of patients, and in our cohort, 4 of 7 patients had confirmed SFN either with a skin biopsy or QSART [17]. Importantly, immunotherapy has been found to be effective in patients with autoimmune or immune-mediated SFN [18].

Our study suggests that SCIG and PLEX may be safe and effective in patients with severe POTS unresponsive to standard pharmacologic and non-pharmacologic therapies. In this study, we excluded patients with POTS who met formal criteria for one or more comorbid autoimmune conditions to describe improvement with SCIG or PLEX in POTS, which is not secondary or associated with defined autoimmune disorders that commonly respond to immunotherapy. Limitations of this study are significant and include retrospective data collection, a small sample size, a lack of control group, and recall bias as some patients were asked to remember and evaluate their symptoms prior to starting immunotherapy. Therefore, it's unknown whether the favorable outcomes of SCIG or PLEX in our case series are generalizable to a larger patient population. Unfortunately, for financial reasons, post-treatment tilt table test and other autonomic function tests were not obtained to objectively verify subjective improvement reported by the patients. Despite these limitations, the case series provides preliminary findings of efficacy and safety of SCIG and PLEX, which should be verified in randomized, controlled trials in patients with severe POTS, unresponsive to standard pharmacologic and non-pharmacologic therapies.

Author contributions KK—conceptualization, data curation, formal analysis, and writing. JS—conceptualization (supporting), formal analysis, and writing—review and editing. SB—conceptualization (lead); formal analysis, writing—review and editing, and supervision.

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Svetlana Blitshteyn takes full responsibility for the data, the analyses and interpretation, and the conduct of the research, has full access to all of the data, and has the right to publish any and all data separate and apart from any sponsor. The data that support the findings of this study are available from Svetlana Blitshteyn upon reasonable request.

Data availability statement Svetlana Blitshteyn takes full responsibility for the data, the analyses and interpretation, and the conduct of the research, has full access to all of the data, and has the right to publish any and all data separate and apart from any sponsor. The data that support the findings of this study are available from Svetlana Blitshteyn upon reasonable request.

Declarations

Conflicts of interest Katrina Kesterson—reports no disclosures or conflicts of interest. Jill Schofield—reports no disclosures or conflicts of interest. Svetlana Blitshteyn—reports no conflicts of interest. Svetlana Blitshteyn has served as a medical expert witness on cases of POTS in the U.S. Court of Federal Claims and for the U.S. Department of Labor.

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