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Intravenous Immunoglobulin Therapy in Refractory Autoimmune Dysautonomias: A Retrospective Analysis of 38 Patients

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Background: Intravenous immunoglobulin (IVIG) has recognized efficacy in autoimmune peripheral nerve disorders, but there has been limited study of the use of IVIG in autoimmune dysautonomias.

Study Question: To determine the efficacy and safety of IVIG in patients with disabling, refractory autoimmune dysautonomias, including patients with postural tachycardia syndrome and gastrointestinal dysmotility.

Study Design: Patients with one or more autonomic disorder(s) and persistent serological evidence for autoimmunity who were unable to work or attend school despite usual treatments for dysautonomia were treated with IVIG for at least 3 months at a dose of at least 1 gm/kg monthly.

Measures and Outcomes: Outcome measures included the composite autonomic symptom scale 31 survey and a functional ability score.

Results: There were 38 patients, 84% female and mean age of 28.4 years. Of patients, 83.5% improved on IVIG as defined by at least 20% improvement in the composite autonomic symptom scale 31 and/or functional ability score. The mean pretreatment functional ability score was 21% (mostly bedridden), which improved to a mean of 74% (nearing able to return to work/school) for responsive patients after at least 1 year of IVIG. The mean time to the first sign of response was 5.3 weeks. There were no serious adverse events. The Mayo autoimmune dysautonomia panel antibodies and traditional Sjögren antibodies were present in only 13% and 8% of patients, respectively, but antiphospholipid antibodies and novel Sjögren antibodies were present in 76% and 42% of patients, respectively.

Conclusions: There is increasing evidence that IVIG is safe and effective in a subset of patients with autonomic disorders and evidence for autoimmunity. A 4-month IVIG trial should be considered in severely affected patients who are refractory to lifestyle and pharmacological therapies. Antiphospholipid antibodies and novel Sjögren antibodies are often present in these patients and correlate with a high response rate to IVIG.

Keywords: antiphospholipid syndrome, dysautonomia, postural tachycardia syndrome, gastrointestinal dysmotility, Sjögren syndrome, intravenous immunoglobulin

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INTRODUCTION

Dysautonomia is an umbrella term that includes different disorders of the autonomic nervous system. The autonomic nervous system is a 3-neuron system, which begins in the primitive areas of the brain, synapses in the spinal cord, and ends in the small fiber

autonomic nerves which innervate every blood vessel, organ, and gland in the body to maintain homeostasis. Pathology anywhere along this pathway may result in symptoms of autonomic dysfunction. In a subset of patients, the pathogenesis is believed to be autoimmune. Centrally, this may occur because of multiple sclerosis[1] or neuromyelitis optica spectrum disorder.[2] Peripherally, it may occur because of an immune-mediated autonomic neuropathy. Dysautonomia may be the initial manifestation of systemic autoimmune disease,[3–5] and there is emerging evidence that autonomic dysfunction may be involved in the etiopathogenesis of systemic autoimmune disease.[6]

Intravenous immunoglobulin (IVIG) therapy is standard of care in the treatment of several inflammatory peripheral nerve disorders,[7,8] and reports of efficacy of IVIG in autoimmune forms of dysautonomia date back to 1996.[9–23] We report our experience with the use of IVIG in 38 patients with severe autoimmune dysautonomias, that is, patients with one or more autonomic disorder occurring in the context of persistent serological and clinical evidence for autoimmunity.

PATIENTS AND METHODS

Study approval

This study was approved by the Institutional Review Board of the University of Colorado.

Patient selection

All patients were seen and evaluated by the first author (J.R.S.) between January 2013 and July 2017. Patients were included regardless of age if they fulfilled each of the following criteria:

1. Diagnosed with one or more of the following autonomic disorders: postural tachycardia syndrome (POTS), orthostatic intolerance, vasovagal syncope, inappropriate sinus tachycardia, gastrointestinal dysmotility, complex regional pain syndrome, and/or neurogenic bladder.
2. Persistent positivity for one or more autoantibodies that have been associated with autonomic dysfunction.
3. Unable to work or attend school regularly despite standard lifestyle and symptomatic pharmacological therapy.
4. Treated with IVIG at a dose of at least 1 gm/kg monthly for at least 3 months.

Autonomic testing

All but 1 patient underwent a head-up tilt test or in-office standing testing. All but 1 patient underwent a quantitative sudomotor axon reflex test and/or skin biopsy to evaluate for small fiber neuropathy using the technique as previously described.[24] POTS was defined as previously described[25] based on symptoms of orthostatic intolerance and an increase in heart rate of at least 30 beats per minute within 10 minutes of upright positioning without evidence of orthostatic hypotension, and orthostatic intolerance was diagnosed if the heart rate increase was 20–29 beats per minute. Vasovagal syncope was diagnosed during tilt table testing if there was a sudden fall in blood pressure and/or heart rate resulting in syncope or near-syncope. Inappropriate sinus tachycardia was diagnosed if average heart rate on continuous cardiac monitoring for at least 24 hours was 90 beats per minute or greater. Severe gastrointestinal dysmotility was defined as dependence on parenteral nutrition or requirement for bowel resection because of toxic megacolon. Neurogenic bladder was defined as dependence on intermittent straight catheterization without evidence for a structural abnormality or infection. Complex regional pain syndrome was diagnosed using the Budapest clinical criteria.[26] Joint hypermobility syndrome (JHS) was defined using the revised Brighton criteria[27] because all patients underwent initial evaluation before the description of the 2017 international classification of the Ehlers-Danlos syndromes.

General testing

All patients underwent a comprehensive evaluation to investigate the etiology of their autonomic disorder including echocardiogram, cardiac monitoring, brain magnetic resonance imaging, catecholamines, cortisol, thyroid function tests, heavy metals, glycosylated hemoglobin, vitamin B12, creatine kinase, aldolase, human immunodeficiency virus, hepatitis C virus and Lyme antibody and/or Western blot analysis, serum protein electrophoresis, and serum light chains. Other testing including cardiac stress testing and spinal magnetic resonance imaging was performed in selected patients.

Autoimmune testing

The following tests were performed in most patients: anticardiolipin immunoglobulin M (IgM), immunoglobulin G (IgG), and immunoglobulin A (IgA); beta-2 glycoprotein IgM, IgG, and IgA; lupus anticoagulant testing; anti-phosphatidylserine IgG, IgM, and IgA; anti-prothrombin IgG; anti-phosphatidylserine-prothrombin IgM and IgG; anti-annexin V IgM and IgG; anti-phosphatidylethanolamine IgM and IgG; novel Sjögren syndrome panel (carbonic anhydrase-6 IgM, IgG, and IgA; parotid secretory protein IgM, IgG, and IgA; salivary protein-1 IgM, IgG, and IgA) by

Immco Diagnostics; anti-tissue transglutaminase IgA and anti-gliadin IgA; thyroid stimulating hormone receptor antibodies, thyroglobulin antibodies, and thyroid peroxidase antibodies; antinuclear antibody testing, including Sjogren syndrome-A (SS-A) IgG, Sjogren syndrome-B IgG, smith IgG, ds-DNA IgG, N-RNP IgG, centromere IgG; rheumatoid factor, anticyclic citrullinated peptide antibodies; and autoimmune dysautonomia panel by Mayo laboratories. Serum immunoglobulins and complements 3, 4 were also performed in most patients. Other antibody testing was performed occasionally as dictated by the clinical presentation. Muscarinic and adrenergic antibody testing was performed by CellTrend GmbH in Germany only in patients with suspected autoimmune dysautonomia who tested negative for other immune markers. Positive results were repeated to confirm accuracy of the result except for the muscarinic and adrenergic antibodies.

IVIG treatment protocol

Most patients were treated using the same treatment protocol. Two patients were started by outside providers at a dose of 1.8 gm/kg every 4–6 weeks. For the others, the starting dose was 1 gm/kg per month given in weekly divided doses, that is, 0.25 gm/kg per week. A loading dose was not used. The initial rate of infusion was 3 gm/h or the slowest rate possible to allow the infusion to be completed during infusion center hours as patients with dysautonomia anecdotally have an increased risk of developing aseptic meningitis with IVIG. A set rate was used, not an uptitration protocol. All patients were given 1 L of normal saline before their infusion to reduce the risk of aseptic meningitis, thrombosis, and renal failure. The rate of infusion was increased by 1 gm/h with subsequent infusions as tolerated, allowing the frequency of infusions to be decreased over time to a single 1 gm/kg infusion monthly for some patients. If after 6–9 months, the patient had not achieved the goal 80%–90% overall functional level, a trial of gradually increasing the dose was considered. The higher dose was maintained only if it provided meaningful improvement. Different IVIG brands were used depending on infusion location.

Outcome measures

Baseline disease severity was determined using the composite autonomic symptom scale 31, a questionnaire evaluating 6 domains of autonomic function, which has been validated in several neurological diseases that may cause autonomic dysfunction.[28] Raw scores were reported ranging from 0 (best) to 75 (worst). All patients were also assessed using an overall functional ability score (Table 1) at baseline and at regular intervals. This 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.[29] Repeat skin biopsy was available for 4 patients after 12 months or more of IVIG therapy.

Data collection/statistical analysis

Data were collected by retrospective chart review, and basic statistical analysis was used.

RESULTS/DISCUSSION

Clinical characteristics of the patients/disability

The clinical characteristics of the patients are shown in Table 2. More than 1 autonomic disorder was seen in 42% of patients, although if milder gastrointestinal dysmotility were included that number would be close to 100%. All patients had progressive disease despite conventional lifestyle/symptomatic pharmacological treatment for their dysautonomia, and most patients were bedridden/nearly bedridden at the time of initiation of IVIG treatment. A similar degree of disability has been described in previous reports of patients with autoimmune dysautonomias.[3,19] Typical of most severe autoimmune diseases, recovery without immune modulatory therapy is not typical, and patients in the

Table 1. Functional ability score.

100%	You feel "normal" most of the time; able to work or attend school full-time without modifications.
90%	You have or feel ready to return to work or attend school full-time with modifications and have or believe you will tolerate this with only mild symptoms most of the time.
80%	You have or feel ready to return to work or attend school part-time with modifications and have or believe you will tolerate this with only mild symptoms most of the time.
70%	You can make social and family commitments most of the time.
60%	You have more good days than bad days.
50%	You are trying to have a normal life, but you still have more bad days than good days.
40%	You get out of bed most of the time and can do more than just "survive."
30%	You are only bedridden a few days a week.
20%	You are mostly bedridden; you can do basic daily tasks, but with great effort.
10%	You are completely bedridden.

Table 2. Clinical characteristics of the patients.

	Age at start of IVIG	Disease duration, yrs	Sex	Cardiovascular autonomic disorder	Other autonomic disorder(s) *	Baseline COMPASS-31 (0–75)	Baseline functional ability score (0–100), %	SGNFD % (Normal ≥ 38.8%)
Responders								
Patient 1	43	2	F	POTS, IST	None	37	30	Abnormal QSART
Patient 2	23	5	M	VVS	CRPS	41	30	28.2
Patient 3	29	6	F	POTS	None	56	10	32.7
Patient 4	52	10	F	Not tested	CRPS	53	10	28.6
Patient 5	48	7	F	POTS	GI dysmotility (toxic megacolon)	38	25	29.1
Patient 6	43	2	M	VVS	None	55	20	19.4
Patient 7	38	9	F	OI	GI dysmotility, neurogenic bladder	48	25	29.1
Patient 8	28	1	F	VVS	None	49	10	29.7
Patient 9	9	3	F	POTS	None	48	40	31.6
Patient 10	52	14	M	POTS	None	30	25	26.7
Patient 11	36	4	F	POTS	None	45	10	29.9
Patient 12	30	4	M	POTS	None	54	40	28.6
Patient 13	28	13	F	IST, VVS	None	41	10	26.3
Patient 14	40	8	F	POTS	None	62	15	31
Patient 15	27	2	F	POTS	CRPS	53	10	17.9
Patient 16	21	3	F	POTS	GI dysmotility	55	15	39.3
Patient 17	30	2	F	POTS	None	62	10	23.4
Patient 18	39	20	F	POTS	CRPS, neurogenic bladder	52	20	30.3
Patient 19	31	4	F	IST	None	36	20	33.7
Patient 20	59	2	F	OI	None	60	20	28.5
Patient 21	36	7	F	POTS	None	46	25	29.2
Patient 22	16	2	F	POTS	GI dysmotility, neurogenic bladder	55	10	abnormal QSART
Patient 23	40	10	F	VVS	None	57	15	33.7
Patient 24	42	2	F	POTS	None	54	15	31.2
Patient 25	48	14	F	POTS	None	41	15	Abnormal QSART
Patient 26	34	4	F	POTS	GI dysmotility	46	30	8.6
Patient 27	15	3	F	POTS	None	46	20	22.1

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Table 2. (*Continued*) Clinical characteristics of the patients.

	Age at start of IVIG	Disease duration, yrs	Sex	Cardiovascular autonomic disorder	Other autonomic disorder(s) *	Baseline COMPASS-31 (0–75)	Baseline functional ability score (0–100), %	SGNFD % (Normal ≥ 38.8%)
Patient 28	14	2	F	POTS	None	37	20	38.6
Patient 29	19	3	F	POTS	None	49	15	28.2
Patient 30	39	13	F	POTS	GI dysmotility, neurogenic bladder	35	10	41
Patient 31	48	1	F	POTS	None	49	30	30.5
Patient 32	17	6	F	POTS	GI dysmotility	49	30	34.9
Mean	33.6	5.9	88% F			48.1	20	29.0
Nonresponders								
Patient 33	20	4	F	POTS	CRPS, GI dysmotility, neurogenic bladder	51	20	27.2
Patient 34	65	7	M	OI	None	32	25	26.5
Patient 35	33	3	F	OI, IST	None	57	35	Not done
Patient 36	36	2	F	POTS	None	65	20	28.8
Patient 37	42	3	F	VVS, OI	None	41	30	30.2
Patient 38	20	4	M	POTS	None	34	15	39.7
Mean	36.0	3.8	67% F			46.7	24	30.5
Overall mean	34	5.6	84% F			47.9	21	29.2

	Autoimmunity	Family history of autoimmune disease †	Hypermobility spectrum disorder/ Ehlers-Danlos syndrome‡	Duration of IVIG, mo	Time to initial response, wk	Maximum IVIG dose, gm/kg per month	Major comorbidities
Responders							
Patient 1	APS, elevated total IgM	Yes	No	53	5	1.3	None
Patient 2	APS, autoimmune hepatitis, uveitis, thyroiditis, positive ANA, elevated total IgM	No	No	24	3	1	None
Patient 3	Early Sjogren's, SS-A, thyroiditis, IgA deficiency	Yes	Yes	19	8	1.1	MCAS§

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Table 2. (*Continued*) Clinical characteristics of the patients.

	Autoimmunity	Family history of autoimmune disease †	Hypermobility spectrum disorder/ Ehlers-Danlos syndrome‡	Duration of IVIG, mo	Time to initial response, wk	Maximum IVIG dose, gm/kg per month	Major comorbidities
Patient 4	APS, early Sjogren's, IgM deficiency	Yes	No	18	8	1.4	None
Patient 5	APS, early Sjogren's, positive ANA, thyroiditis	No	No	18	6	1.8	Refractory ischemic colitis and lower extremity ulcers
Patient 6	APS, early Sjogren's, Crohns disease, elevated total IgA	Yes	No	17	8	1.3	MCAS
Patient 7	APS	Yes	Yes	16	5	1.7	None
Patient 8	APS, DM1, thyroiditis, anti-68 kd Ab, GAD 65 Ab, positive ANA, alopecia areata	Yes	No	16	8	1	None
Patient 9	APS, early Sjogren's, thyroiditis	Yes	Yes	15	2	1	Stroke, transient cerebral ischemia
Patient 10	Muscarinic 4 receptor Abs, positive ANA, thyroiditis	No	No	14	8	1.2	MCAS
Patient 11	APS, early Sjogren's, positive ANA, elevated total IgA, elevated total IgG	Yes	No	13	8	1.0	None
Patient 12	APS, GAD 65 Ab, thyroiditis, positive ANA	No	No	13	4	1	None
Patient 13	APS, IgG deficiency	Yes	Yes	12	6	1	Refractory idiopathic granulomatous mastitis
Patient 14	VGKC Ab	Yes	Yes	12	5	1	MCAS
Patient 15	APS, ganglionic AChR Ab, positive ANA, early Sjogren's	No	No	10	4	1.1	None
Patient 16	APS, early Sjogren's, thyroiditis, celiac disease, IgE receptor Ab	Yes	Yes	8	11	1	None

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Table 2. (*Continued*) Clinical characteristics of the patients.

	Autoimmunity	Family history of autoimmune disease †	Hypermobility spectrum disorder/ Ehlers-Danlos syndrome‡	Duration of IVIG, mo	Time to initial response, wk	Maximum IVIG dose, gm/kg per month	Major comorbidities
Patient 17	RA, early Sjogren's, celiac disease, thyroiditis, positive ANA, autoimmune hepatitis	Yes	No	7	3	1.2	None
Patient 18	APS	Yes	No	6	1	1	Refractory disseminated zoster
Patient 19	APS, celiac disease, early Sjogren's, positive ANA	No	No	6	8	1	None
Patient 20	APS, SS-A, early Sjogren's, positive ANA, positive ANCA, elevated total IgA	Yes	No	6	6	1.8	None
Patient 21	APS, early Sjogren's, IgA deficiency	Yes	Yes	5	5	1	None
Patient 22	early Sjogren's; IgE receptor Ab	Yes	Yes	5	5	1	MCAS; recurrent infections; IIH
Patient 23	APS	Yes	No	5	2	1	Stroke
Patient 24	APS, early Sjogren's, IgE receptor Ab	No	No	5	5	1	MCAS
Patient 25	APS, IgA deficiency, IgG3 subclass deficiency	No	No	5	5	1	None
Patient 26	Early Sjogren's	Yes	No	4	12	1	None
Patient 27	Muscarinic and adrenergic receptor antibodies	Yes	Yes	4	2	1	None
Patient 28	APS, early Sjogren's, positive ANA, IgE receptor Ab, elevated total IgA	Yes	Yes	3	3	1	None
Patient 29	APS, positive ANA	Yes	Yes	3	4	1	Craniocervical instability, MCAS

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Table 2. (*Continued*) Clinical characteristics of the patients.

	Autoimmunity	Family history of autoimmune disease †	Hypermobility spectrum disorder/ Ehlers-Danlos syndrome‡	Duration of IVIG, mo	Time to initial response, wk	Maximum IVIG dose, gm/kg per month	Major comorbidities
Patient 30	APS, early Sjogren's, thyroiditis, IgE receptor Ab, IgA deficiency	Yes	No	3	4	1	Recurrent sepsis
Patient 31	APS, early Sjogren's, Psoriatic arthritis, uveitis, lupus, IgG deficiency	Yes	Yes	3	2	1	Recurrent infections
Patient 32	APS, early Sjogren's, ITP	Yes	No	3	3	1.2	MCAS, MALS
Mean		75%	38%	11.0	5.3	1.1	47%
Nonresponders							
Patient 33	APS, positive ANA, IgG deficiency, elevated total IgM	Yes	Yes	6	No response	1	MCAS
Patient 34	APS, early Sjogren's, thyroiditis	Yes	No	6	No response	1.1	None
Patient 35	GAD65 Ab, alopecia areata	No	Yes	6	No response	1.1	None
Patient 36	APS, early Sjogren's, SS-A, thyroiditis, elevated total IgM, positive ANA	Yes	No	5	No response	1	MCAS
Patient 37	APS, SS-A, positive ANA	No	No	5	No response	1	None
Patient 38	Positive ANA, positive RNP, folate receptor antibodies	Yes	No	4	No response	1	MCAS
Mean		66%	33%	5.3	N/A	1.0	50%
Overall mean		74%	37%	10.1		1.1	47%

*GI dysmotility listed only in patients requiring artificial nutrition; less severe GI dysmotility was present in most patients; neurogenic bladder listed only in patients requiring catheterization; less severe bladder dysfunction was present in some patients.

†Parent, sibling, and/or grandparent.

‡Defined using the Brighton criteria for joint hypermobility syndrome as all patients underwent initial evaluation before the description of the 2017 international criteria for the Ehlers-Danlos syndromes.

§Only patients with a serologically proven diagnosis of MCAS were included; several others had a suspected diagnosis of MCAS.

Ab, antibody; AChR, acetylcholine receptor; ANA, antinuclear antibody; APS, antiphospholipid syndrome/antibodies; COMPASS, Composite Autonomic Symptom Scale; CRPS, complex regional pain syndrome; DM1, type I diabetes mellitus; GAD, glutamic acid decarboxylase; GI, gastrointestinal; IgE, immunoglobulin E; IIH-idiopathic intracranial hypertension; IST, inappropriate sinus tachycardia; ITP, immune thrombocytopenia; MALS, median arcuate ligament syndrome; MCAS, mast cell activation syndrome; OI, orthostatic intolerance; RNP, ribonuclear protein; SGNFD, sweat gland nerve fiber density; VGKC, voltage-gated potassium channel; VVS, vasovagal syncope.

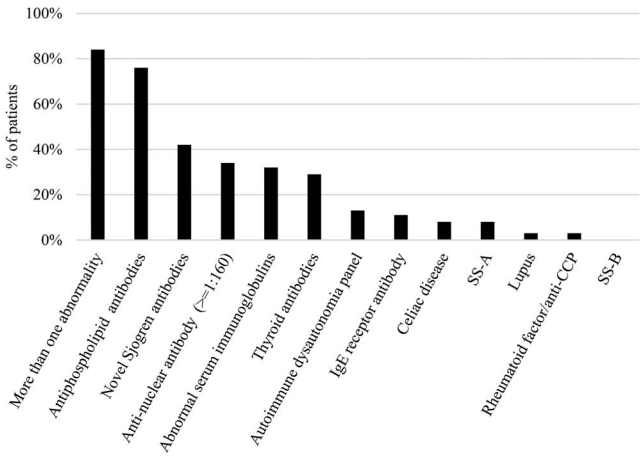

FIGURE 1. Incidence of autoimmune abnormalities in the patients. IgE, immunoglobulin E; SS-A, Sjogren syndrome A IgG; CCP, cyclic citrullinated peptide antibody; SS-B, Sjogren syndrome B IgG.

present study had been ill an average of 5.6 years before starting IVIG, highlighting the difficulty these patients have in getting the proper diagnosis and treatment, as well as the failure to recover.

Autoimmune phenotype

The incidence of different autoimmune markers/diseases is shown in Figure 1. There was not a unique antibody phenotype; rather, there was often evidence for widespread immune dysregulation with 84% of patients having more than 1 category of immune dysfunction. The antibodies typically ordered in clinical practice to evaluate for a possible autoimmune cause for dysautonomia were not present in most of our patients, including the Mayo laboratories autoimmune dysautonomia panel (13%), traditional Sjögren antibodies SS-A (8%), Sjogren syndrome-B (0%), and rheumatoid factor (3%). Rather, antiphospholipid antibodies (76%) and novel Sjögren antibodies (42%) were common and often coexisted. All patients with these antibodies had systemic features of those diseases, both of which have been associated with dysautonomia.[3,4,15,21,30,31] As is seen with many autoimmune diseases, some patients tested positive only for a single antiphospholipid or Sjögren antibody type, whereas others tested positive for multiple antibodies, but the clinical phenotype and the response to IVIG did not seem to correlate with antibody number, titer, or subtype.

Comorbidities

Fourteen of 38 (37%) patients met the revised Brighton criteria for JHS, which is similar to the proportion of all patients with POTS who have underlying JHS.[32] Eighteen of 38 (47%) patients had one or more significant comorbidities that may have negatively affected their degree of response to IVIG.

Response to IVIG

Our overall response rate of 83.5% confirms the results recently published in 55 patients with "apparently autoimmune" polyneuropathy in which 77% of neurologists reported the patient as an "IVIG responder"[23] and are similar to those previously published in smaller case series.[19,20] Because the response to IVIG is typically gradual in this patient population, detailed analysis of the response is shown only for patients who were treated with IVIG for at least 12 months. The pre- and postcomposite autonomic symptom scale 31 and functional ability scores for these patients are shown in Figures 2 and 3, respectively. Despite a high degree of disability in these patients, IVIG was dramatically effective in some, a few of whom achieved a near-normal functional ability. Importantly, patients with disease duration up to 20 years still responded to treatment. The time in weeks for the patient to notice their first signal of benefit from IVIG treatment is shown in Figure 4. This was a patient-reported subjective measure. The average time to the first sign of improvement was 5.3 weeks, but 2 patients did not show improvement until 11–12 weeks. Thus, a 4-month trial of IVIG is usually adequate to determine response in this clinical context. The delay in response to IVIG in our study suggests that the response is not related to the pre- and/or post-IVIG use of normal saline given to reduce the risk of aseptic meningitis, thrombosis, and nephrotoxicity. Indeed, several of the patients were treated with up to 2 L of normal saline daily as a bridge to IVIG, and their pre-IVIG baseline was assessed while receiving regular intravenous hydration.

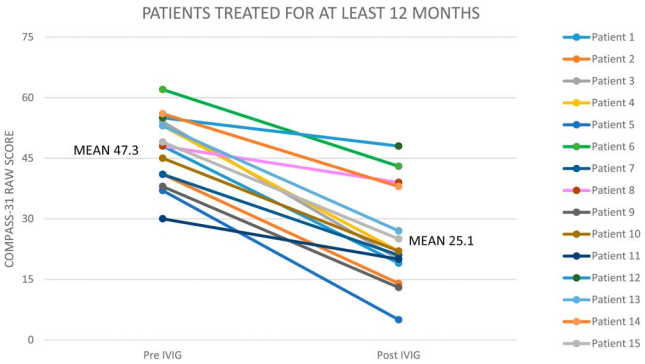

FIGURE 2. COMPASS-31 scores (0 = best; 75 = worst) at baseline and at the end of the treatment period for the patients treated with IVIG for at least 12 months.

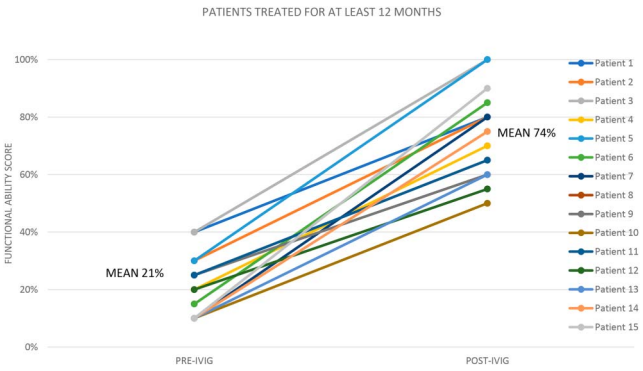

FIGURE 3. Functional ability scores (0%–100%) at baseline and at the end of the treatment period for the patients treated with IVIG for at least 12 months.

A detailed timeline of response is provided in Figures 5 and 6 for the 2 patients treated the longest, illustrating that a patient's maximal response may require well more than 1 year of treatment. This may be due to gradual healing of small fiber nerves. Five responsive patients had their treatment interrupted for insurance or other reasons, all within the first year of treatment. All experienced significant clinical deterioration, but each responded when IVIG was reinitiated. Skin biopsy was repeated in 4 patients who had received at least 1 year of therapy. There was significant improvement in sweat gland and/or epidermal nerve fiber density in 2 of the 4 patients. Because this invasive procedure did not seem to correlate with objective improvement in some patients at the 1 year mark, it was not continued.

Need for a reliable biomarker of disease

Lack of improvement in the epidermal and/or sweat gland nerve fiber density in 2 of 4 patients despite a clear clinical response to IVIG, combined with evidence of functional improvement after many years of disease in some patients, suggests that reversible neural receptor autoantibodies that impair autonomic function may play

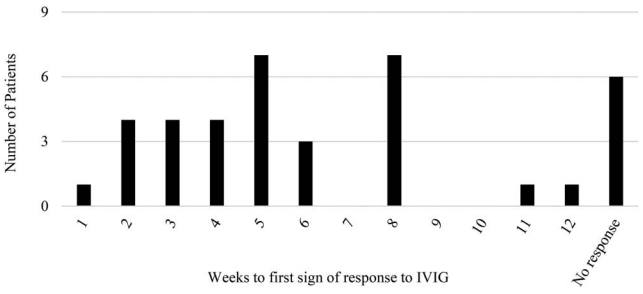

FIGURE 4. Time in weeks to the first patient-reported sign of response to IVIG.

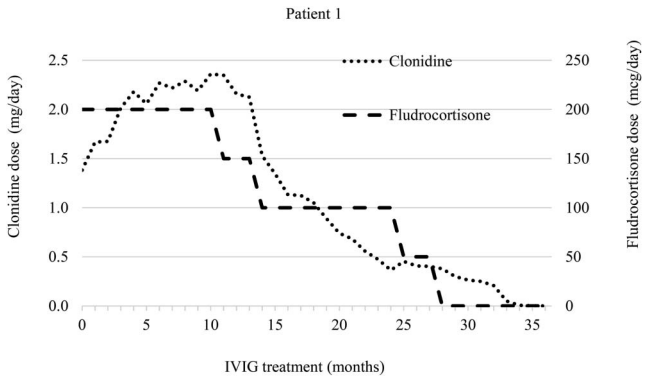

FIGURE 5. Timeline of response to IVIG in patient 1. Clonidine and fludrocortisone doses over time after initiation of treatment with IVIG. This patient had an extremely hyperadrenergic variant of postural tachycardia syndrome requiring high doses of clonidine and Florinef. After initiation of IVIG, she was gradually able to taper off both clonidine and Florinef. Symptomatic improvement preceded blood pressure improvement. Anecdotally, patients with dysautonomia with labile hypertension often have antiphospholipid antibodies, and this was reported in the initial descriptions of the antiphospholipid syndrome.[3]

a more important pathogenic role than damage to autonomic nerves in some patients. Alternatively, skin biopsy may not be an adequate biomarker of this disease. Our unpublished data (K.R.C.) suggest that repeat autonomic function testing results after IVIG also do not consistently parallel clinical improvement. Because IVIG is

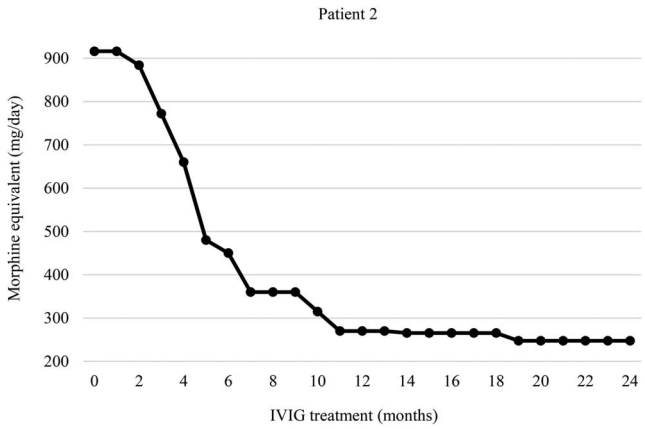

FIGURE 6. Time line of response to IVIG in patient 2. Daily narcotic dose over time after initiation of treatment with IVIG. This patient had complex regional pain syndrome in addition to vasovagal syncope. He met the formal classification criteria for antiphospholipid syndrome with a history of arterial thrombosis. All 5 of the patients in the present report with complex regional pain syndrome had thrombotic antiphospholipid syndrome.

not an immune-suppressing therapy and is composed of pooled IgG molecules that can interfere with IgG antibody testing, following antibody titers is not likely to be helpful in patients treated with IVIG. Lack of a reliable biomarker has hindered diagnosis and research in this area.

Nonresponders

There was not a statistically significant difference between IVIG responders and nonresponders in terms of age, duration of disease, baseline disease severity, antibody profile, or comorbidities.

Toxicity

One patient developed presumed aseptic meningitis requiring an emergency department visit when the described graduated protocol was not followed by an outside provider; the patient quickly improved with Decadron and intravenous hydration. One patient developed transaminitis with liver function tests of 5 times the upper limit of normal with an increase in IVIG dose to 1.5 gm/kg monthly. Liver function tests quickly normalized by decreasing the dose back to the previously tolerated dose and no doses were missed. A few patients developed a flare of comorbid mast cell activation syndrome, with most or all infusions requiring high doses of antihistamines and occasionally steroids. We have found that preparation of IVIG in a glass bottle rather than a plastic bag may decrease mast cell reactivity. Importantly, no patient developed a thrombotic event, but all patients testing positive for antiphospholipid antibodies were treated with antiplatelet and/or anticoagulation therapy. No patient developed nephrotoxicity or a severe infusion reaction. Most patients developed nuisance symptoms including headache, neck pain, fatigue, and myalgias. These manifestations lasted up to a few days postinfusion and improved with time for most patients. Worsening of hypertension, hypotension, and tachycardia was also seen in a few patients and improved with time in all patients. Scheduled nonsteroidal anti-inflammatory agents, antihistamines, and/or a second liter of normal saline postinfusion were helpful to reduce symptoms.

The emerging link between the immune system and the autonomic nervous system

There is an emerging link between the autonomic nervous system and the immune system, and chronic autonomic dysfunction is suspected to play a role in the etiopathogenesis of systemic autoimmune disease.[6] This may explain why widespread immune dysregulation rather than a specific autoimmune phenotype is seen in these patients and why dysautonomia may be seen in the context of many systemic autoimmune diseases.[33] The first pathway described linking the autonomic nervous system and the immune system was the anti-inflammatory cholinergic pathway in which activation of the vagus nerve leads to a decrease in the production of tumor necrosis factor from splenic macrophages.[34] There are suspected to be other pathways linking these systems, and interaction between the small fiber autonomic nerves and mast cells may explain why many of these patients also have mast cell activation syndrome.

Suggested approach to the diagnosis and treatment of autoimmune dysautonomias

In recent years, several studies have reported an increased incidence of autoimmune markers and/or autoimmune disorders in patients with dysautonomia.[35] There are many causes of dysautonomia, however, and the patients in the present report represent only a subset. Whether to test all patients with dysautonomia for autoimmunity is debatable as some patients achieve a near-normal functional ability with conventional lifestyle and symptomatic pharmacologic treatments, but there are important implications for patients with autoimmunity. Progression of disease despite symptomatic treatment, as well as severely disabling disease should increase suspicion for an autoimmune cause, as should a personal history of autoimmunity or clinical features that may be seen in systemic autoimmune diseases, including the Raynaud phenomenon, livedo reticularis, refractory migraine, thrombosis, pregnancy morbidity, thrombocytopenia, malar rash, inflammatory arthritis, alopecia, and/or an abnormal Schirmer test (not seen in most patients with dysautonomia per anecdotal experience, J.R.S.). A family history of autoimmune disease was present in 74% of the present patients; this is much higher than the 8%–10% incidence of autoimmune disease seen in the general population and should also suggest a possible autoimmune cause as should onset of illness after one of the recognized triggers of autoimmunity (infection, vaccination, concussion, surgery, trauma, or pregnancy).

Current tests for autoimmune causes of dysautonomia are noted in the section Autoimmune testing. Adrenergic and muscarinic receptor antibody testing is presently commercially available only in Germany; early studies suggest that these antibodies may play an important role in the pathogenesis of dysautonomia[36] and the results of ongoing studies are eagerly awaited. An alternative hypothesis is that they may be natural antibodies involved in the normal regulation of autonomic tone. We suggest a lower threshold to test for

antiphospholipid, Sjögren, celiac, and thyroid antibodies because the presence of these antibodies may change management even if the severity of disease does not justify a trial of IVIG. If antiphospholipid antibodies are present, avoidance of exogenous estrogen, high-risk obstetric care, awareness of increased thrombotic risk and consideration of therapy with hydroxychloroquine, and/or antithrombotic therapy are appropriate. The presence of the SS-A antibody has important pregnancy implications, and hydroxychloroquine often results in symptomatic improvement in Sjögren syndrome. Thyroid antibodies can be seen in the context of hypothyroidism but also in the absence of thyroid function abnormalities and signal the need to monitor thyroid function tests regularly and identify risk of comorbid autoimmune conditions. Finally, a gluten-free diet reduces mortality in patients with celiac disease.[37] Of note, celiac disease has been described in association with autonomic neuropathy[38]; however, all 3 of our patients with celiac disease had other disease-specific antibodies that seem more likely to explain the associated dysautonomia, but the specific mechanism by which autoimmunity leads to autonomic dysfunction has not been determined for any of these diseases. The presence of antineuronal antibodies may not change management except in patients who are appropriate for a trial of immunomodulatory therapy, but these antibodies can be paraneoplastic and should also be considered when there is concern for malignancy. We only recommend IVIG in patients with severe disease, given the expense, burden, and potential risks of the therapy. In addition to those with disease-specific antibodies that have been associated with autonomic dysfunction, our data suggest that a 4-month trial of IVIG should be considered in patients with disabling, refractory dysautonomia who have a positive antinuclear antibody, thyroid antibodies, and/or abnormal serum immunoglobulins because these markers often coexist with presumed pathogenic antibodies and suggest an autoimmune cause of dysautonomia.

The concept of seronegativity has proven to be important in most autoimmune diseases. There has been an explosion of clinically important novel antibodies described over the past decade, particularly in neurological diseases, and many of these are not yet commercially available. It is essential to consider the overall clinical phenotype together with objective testing, recognizing limitations in antibody testing. Several of our patients do not meet formal classification criteria for antiphospholipid syndrome or SS because of the presence of novel antibodies, but these antibodies are associated with disabling disease and a high response rate to IVIG.

CONCLUSIONS

Our findings that IVIG is effective and safe in patients with autoimmune dysautonomias corroborate those of a recently published case series of 55 patients with "apparently autoimmune" small fiber polyneuropathy,[23] as well as those from smaller case series/reports of confirmed or suspected autoimmune small fiber polyneuropathy.[9–21] There is an emerging link between the autonomic nervous system and the immune system, and we have shown that patients with autoimmune dysautonomias often have widespread immune dysregulation and that antibodies typically ordered to evaluate for a possible autoimmune etiology for dysautonomia are not as prevalent as antiphospholipid antibodies and the novel Sjögren antibodies. Our study has important limitations, including its retrospective and single-center design, but our results together with those of Liu et al support a 4-month trial of IVIG in patients with refractory dysautonomia and evidence for autoimmunity. It should be emphasized that the patients included in the present report represent only a subset of all patients with dysautonomia. Prospective studies on the use of IVIG in patients with autonomic disorders are warranted, given the disabling nature of these disorders.

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