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Autonomic neuropathy—in its many guises—as the initial manifestation of the antiphospholipid syndrome

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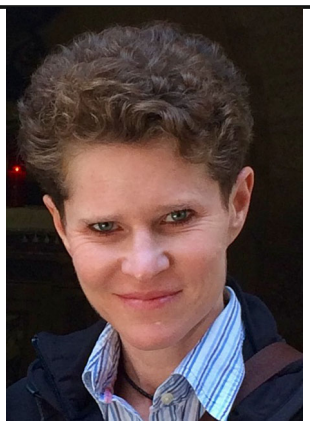

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Abstract Autonomic disorders have previously been described in association with the antiphospholipid syndrome. The present study aimed to determine the clinical phenotype of patients in whom autonomic dysfunction was the initial manifestation of the antiphospholipid syndrome and to evaluate for autonomic neuropathy in these patients. This was a retrospective study of 22 patients evaluated at the University of Colorado who were found to have a disorder of the autonomic nervous system as the initial manifestation of antiphospholipid syndrome. All patients had persistent antiphospholipid antibody positivity and all patients who underwent skin biopsy were found to have reduced sweat gland nerve fiber density suggestive of an autonomic neuropathy. All patients underwent an extensive evaluation to rule out other causes for their autonomic dysfunction. Patients presented with multiple different autonomic disorders, including postural tachycardia syndrome, gastrointestinal dysmotility, and complex regional pain syndrome. Despite most having low-titer IgM antiphospholipid antibodies, 13 of the 22 patients (59%) suffered one or more thrombotic event, but pregnancy morbidity was minimal. Prothrombin-associated antibodies were helpful in confirming the diagnosis of antiphospholipid syndrome. We conclude that autonomic neuropathy may occur in association with antiphospholipid antibodies and may be the initial manifestation of the syndrome. Increased awareness of this association is important, because it is associated with a significant thrombotic risk and a high degree of disability. In addition, anecdotal experience has suggested that antithrombotic therapy and intravenous immunoglobulin therapy may result in significant clinical improvement in these patients.

Keywords Autonomic neuropathy · Antiphospholipid syndrome · Postural tachycardia syndrome · Gastrointestinal dysmotility · Complex regional pain syndrome · Intravenous immunoglobulin

Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder associated with the persistent presence of antiphospholipid antibodies and an increased risk of arterial, venous, and small vessel thromboses. In his initial description of the syndrome, Hughes referred to APS as a "cerebral disease [1]." Subsequently, APS has been associated with a large number of neurological manifestations, including not only stroke but also migraine, memory loss, seizure disorder, chorea, multiple sclerosis-like syndrome, and neuropathy [2, 3].

Labile hypertension without associated renal disease was mentioned in early reports [4], but the first formal association of APS with dysfunction of the autonomic nervous system came in 1999 when Tsutsumi et al. reported reflex sympathetic dystrophy (now known as complex regional pain syndrome) in a patient with APS [5]. In 2012, Bilora et al. demonstrated abnormal autonomic function testing in APS patients without any other autoimmune or cardiovascular disease [6] and in 2013, Garcia et al. reported impaired cardiac autonomic control as well as impaired aerobic exercise capacity in APS patients [7]. In 2014, the association of a number of autonomic disorders in APS was reported, including postural

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tachycardia syndrome, neurocardiogenic syncope, orthostatic hypotension, inappropriate sinus tachycardia, and complex regional pain syndrome [8]. In 2015, Blitshteyn reported a series of 100 consecutive patients with postural tachycardia syndrome and found that 7% had at least one antiphospholipid antibody [9], suggesting this may be a common association.

We detail here a series of 22 patients in which autonomic nervous system disease was the initial presentation of APS. We also demonstrate that despite varied autonomic manifestations, autonomic neuropathy was present in all patients undergoing skin biopsy at multiple sites.

Methods

This is a retrospective, chart review study of 22 patients evaluated at the University of Colorado by the author between June 2015 and April 2016 who were seen in either the dysautonomia clinic or the antiphospholipid syndrome clinic. Due to the author's interest in autoimmune dysautonomia, many patients seen in the dysautonomia clinic have been selected for those more likely to have an autoimmune cause and might represent an even more select population than other tertiary centers' dysautonomia clinics. Sixteen patients who presented with an autonomic disorder tested positive for antiphospholipid antibodies on two occasions at least 12 weeks apart and had evidence for an autonomic neuropathy by skin biopsy. The remaining six patients previously diagnosed with APS were subsequently found to have an autonomic neuropathy on skin biopsy that on questioning was symptomatic before any other manifestations of APS but had gone undiagnosed. The study was approved by the Institutional Review Board of the University of Colorado Anschutz Medical Campus.

All patients underwent a comprehensive evaluation to investigate the etiology of their autonomic disorder including the following: echocardiogram, cardiac monitoring for a minimum of 24 h, brain MRI with gadolinium, serum catecholamines, serum cortisol, serum ACE level, thyroid function tests, serum heavy metals, glycosylated hemoglobin, vitamin B12, creatine kinase, aldolase, erythrocyte sedimentation rate, C-reactive protein, HIV, HCV, Lyme, and treponemal antibodies, serum protein electrophoresis, serum light chains, serum immunoglobulins, urinalysis, autoimmune dysautonomia panel, antinuclear antibody testing by immunofluorescence including SS-A IgG and SS-B IgG, smith IgG, ds-DNA IgG, N-RNP IgG, and centromere IgG, C3, C4, RF, anticyclic citrullinated peptide, antineutrophil cytoplasmic antibodies, tissue transglutaminase IgA, antigliadin IgA, thyroid-stimulating hormone receptor antibodies, thyroglobulin antibodies, and thyroid peroxidase antibodies. Cardiac stress testing was performed if there was significant chest pain and cervical spine MRI (with flexion and extension views in select patients) was performed if there was reason to suspect possible cervical spine or cord disease. Serum tryptase and 24-h urine for 5-HIAA were performed in addition to catecholamines in patients with flushing. Serum and urine porphyrins were obtained in patients with episodic severe abdominal pain. In addition, all skin biopsies were stained with Congo Red to evaluate for amyloidosis.

The diagnosis of APS was determined by the presence of one or more antiphospholipid antibodies on more than one occasion at least 12 weeks apart as well as one or more clinical manifestations of the syndrome. Not all of the present patients met the 2006 revised Sapporo classification criteria for a diagnosis of definite APS, which requires medium- to high-titer antibody levels and thrombosis or specific pregnancy morbidity [10]. These classification criteria, however, were designed to create a homogeneous population for research, not for diagnosis, and patients with low-titer antibody positivity were included in the present study as were patients without a history of thrombosis who had well-described nonthrombotic manifestations of the syndrome. The following tests were performed on all patients: lupus anticoagulant, anticardiolipin IgG and IgM, and antibeta 2 glycoprotein I IgG and IgM. The majority of patients were also tested for the following secondary antiphospholipid antibodies: anticardiolipin IgA, antibeta 2 glycoprotein I IgA, antiphosphatidylserine IgG, IgM and IgA, antiprothrombin IgG and IgM, and antiphosphatidylserine-prothrombin IgG and IgM. All antiphospholipid antibody ELISA testing was performed using INOVA assays, except for the antiprothrombin IgG and IgM testing which was performed by ARUP.

Eighteen of 22 patients underwent formal tilt table testing. The two young children and one adult underwent stand testing. Patient 3 did not have significant cardiac symptoms so tilt table testing was not performed. Postural tachycardia syndrome was diagnosed as previously described [11] based on the presence of symptoms of orthostatic intolerance and an increase in heart rate of at least 30 bpm (or 40 bpm if under age 18) within 10 min of tilt table testing without evidence of orthostatic hypotension. Neurocardiogenic syncope was diagnosed during tilt table testing if there was a sudden fall in blood pressure, heart rate, and cerebral perfusion resulting in loss of consciousness. Inappropriate sinus tachycardia was diagnosed if the resting heart rate was >100 bpm and the average heart rate on 24-h Holter monitoring was >90 bpm. Labile hypertension was diagnosed if there were frequent systolic blood pressures >140 and frequent diastolic blood pressures >90, as well as systolic blood pressures <100, and if renal artery stenosis and pheochromocytoma were excluded. Complex regional pain syndrome was diagnosed using the Budapest criteria as previously described [12]. Severe gastrointestinal dysmotility was defined by delayed gastric emptying and a requirement for artificial nutritional support for maintenance of body weight or the development of toxic

megacolon requiring colectomy. Neurogenic bladder was diagnosed if there was urinary retention requiring intermittent selfcatheterization in the absence of structural abnormalities or culprit medications.

All but one patient underwent skin biopsy to evaluate for small fiber sensory and autonomic neuropathies using the technique as previously described [13]. A 3-mm punch biopsy was obtained from the skin at more than one site (usually the lower leg and lower thigh) and stained with a monoclonal antibody against a protein abundant in all neurons (protein gene product 9.5), allowing the small fibers to be visualized, counted, and quantitated as "nerve fiber density." Small fibers that localized to sweat glands as determined by tyrosine hydroxylase staining were presumed to be autonomic [14]; the others were presumed sensory. Data were normalized to age- and gender-matched controls and were considered abnormal if nerve fiber density was less than 95% of the norm as per consensus guidelines [15]. All biopsy specimens were processed and analyzed by the Corinthian Reference Laboratory, Fort Worth, Texas.

Statistical analysis of the data was performed using Fisher's exact test and statistical significance was defined as a p value <0.05.

Results

Twenty-two patients with APS were identified in which an autonomic disorder was the initial manifestation of the syndrome. The clinical characteristics of these patients are shown in Tables 1 and 2. Most (86%) of the patients were female with an average age of symptom onset of 26.5 (range 6–48) years. Consistent with our original publication, migraine, memory loss, livedo reticularis, and Raynaud's phenomenon were all common. Thirteen of the 22 patients (59%) had one or more thrombotic event an average of 4.4 years after the onset of their autonomic nervous system disease. Both arterial and venous events were seen. Only nine females in our series ever attempted pregnancy. Five of these suffered a fetal loss, but four of five were in the first trimester and all but one patient had at least one live birth. Only one patient met classification criteria for obstetric APS. Seven patients (32%) had an underlying joint hypermobility syndrome and there was a significantly reduced incidence of arterial thrombosis seen in these patients but a higher incidence of small fiber sensory neuropathy when compared to the patients without joint hypermobility. Comorbid autoimmune disease was seen in 36%, most commonly thyroiditis, but no patient had lupus. Autonomic disease in APS was found to be disabling with 89% of the patients who had worked outside the home becoming unable to work due to their autonomic disorder.

As shown in Table 3, multiple different autonomic disorders were seen, including postural tachycardia syndrome, neurocardiogenic syncope, inappropriate sinus tachycardia, labile hypertension, complex regional pain syndrome, severe gastrointestinal dysmotility, and neurogenic bladder, and 45% of the patients had more than one autonomic disorder. Table 4 shows that most patients had low-titer IgM antibodies and that prothrombin-based antibody testing was helpful in confirming the diagnosis of APS. All patients tested for prothrombin-associated antibodies had more than one antibody. As shown in Table 5, all but one patient underwent skin biopsy at multiple sites (usually the distal and proximal legs) and all had reduced sweat gland nerve fiber density at all sites consistent with an autonomic neuropathy. Fifteen of the 21 patients (71%) also had reduced small fiber sensory nerve fiber density—some in a length-dependent pattern and some in a nonlength dependent pattern. Figure 1 shows illustrative skin biopsy images demonstrating normal and reduced sweat gland nerve fiber densities.

Discussion

APS has been estimated to affect at least 1% of the population [16], but it is underrecognized and underdiagnosed. Since the original description of APS in 1983, the focus of the syndrome has been on the thrombotic and pregnancy complications, yet as shown here, "nonthrombotic" manifestations such as autonomic neuropathy can be equally devastating.

It has been estimated that 90% of the autonomic nervous system is comprised of postganglionic small fiber nerves (thinly myelinated A-delta and unmyelinated C fibers). Small fiber sensory nerves transmit pain, itch, and temperature sense, while the autonomic small fibers transmit complex signals from the autonomic ganglia to all blood vessels and internal organs in order to maintain homeostasis. Not surprisingly, dysfunction of the autonomic nervous system results in widespread effects. Cardiovascular autonomic dysregulation causes cerebral hypoperfusion resulting in nausea, dizziness, weakness, fatigue, cognitive dysfunction, and presyncope or syncope upon assumption of an upright posture. Sympathetic overactivation often results which may cause tremulousness, anxiety, and tachycardia. Other systems are also affected, including the stress response and the ability to regulate blood volume, temperature, and digestion. Importantly, the ability to respond to even minor perturbations becomes impaired and "stressors" such as standing, engaging in conversation, or responding to minor changes in traffic can trigger severe and prolonged symptoms, contributing to the disability often seen in patients with autonomic disorders.

Dysfunction of the autonomic nervous system is difficult to diagnose as clinical manifestations are protean and testing is suboptimal. Tilt table or stand testing may be performed to assess for dysregulation of cardiovascular autonomic function, but vital signs checked in the supine or sitting position

Table 1 Clinical characteristics of the patients

	Age	Sex	Autonomic disorder(s)	Thrombotic event(s)	Time from autonomic symptoms to thrombotic event	Pregnancy loss (trimester)	Live birth	Other APS manifestations/ associations	Migraine	Memory loss	Livedo reticularis	Raynaud	Other autoimmune disease	JHS/ EDS	Disability
1	24	F	CRPS, POTS, labile HTN, neurogenic bladder (catheter)	Stroke, PE	8 years	N/A	N/A	Recurrent stress fractures, skin ulcers, PFO, thrombocytopenia. CNS white matter change	Yes	Yes	Yes	Yes	No	No	Yes
2	16	F	CRPS, POTS, GI dysmotility (TPN), neurogenic bladder (catheter)	Recurrent DVT	1.5 years	N/A	N/A	Recurrent stress fractures	Yes	No	Yes	Yes	No	Yes	Yes
3	42	F	CRPS	Stroke, MI, PE	0 years	2 (1st/1st)	0	CAPS × 2, thrombocytopenia, CNS white matter change	Yes	Yes	No	No	No	No	Yes
4	23	M	CRPS, NCS (PM)	Radial artery thrombosis	4.5 years	N/A	N/A	MV thickening	Yes	Yes	Yes	Yes	AIH, uveitis, thyroiditis	No	Yes
5	16	F	NCS	Iliac artery thrombosis, splenic infarction, PE	17 years	1 (2nd)	3	Focal arterial stenosis (iliac)	Yes	Yes	Yes	Yes	No	No	Yes
6	6	F	POTS	Stroke, recurrent TIA	2 years	N/A	N/A	Focal arterial stenosis (carotid)	Yes	Yes	Yes	Yes	Retinal vasculitis, thyroiditis	No	N/A
7	18	M	NCS	DVT, amaurosis fugax, thrombophlebitis	10 years	N/A	N/A	None	Yes	Yes	Yes	Yes	Crohn's disease	No	Yes
8	27	F	POTS, IST	Stroke	2 years	2 (1st/1st)	5	PFO, carotid/vertebral artery dissection[a]	Yes	Yes	Yes	Yes	No	No	Yes
9	32	F	POTS	Amaurosis fugax	1.5 years	N/A	N/A	Retinal vasculitis	Yes	Yes	Yes	Yes	Sjogren's syndrome thyroiditis	No	Yes
10	42	F	POTS, labile HTN	TIA	0.5 years	None	2	Recurrent stress fractures	Yes	Yes	Yes	Yes	No	No	Yes
11	48	F	GI dysmotility (toxic megacolon/-colectomy), POTS	BRVO	7 years	None	2	Skin ulcers, intermittent hearing loss, vertigo, CNS white matter change	Yes	Yes	Yes	Yes	No	No	Yes
12	42	F	POTS	Stroke	0.3 years	1 (1st)	1	PFO, CNS white matter change	Yes	Yes	No	Yes	No	No	Yes
13	38	F	POTS	Superficial venous thrombosis	3 years	None	4	Thrombocytopenia, CNS white matter change	Yes	Yes	Yes	Yes	No	Yes	N/A

Table 1 (continued)

	Age	Sex	Autonomic disorder(s)	Thrombotic event(s)	Time from autonomic symptoms to thrombotic event	Pregnancy loss (trimester)	Live birth	Other APS manifestations/ associations	Migraine	Memory loss	Livedo reticularis	Raynaud	Other autoimmune disease	JHS/ EDS	Disability
14	26	F	GI dysmotility (TF), POTS, NCS	None	N/A	N/A	N/A	None	Yes	No	No	No	Thyroiditis, celiac disease	Yes	No
15	32	F	POTS, labile HTN	None	N/A	1 (1st)	2	CNS white matter change	Yes	Yes	Yes	Yes	No	No	Yes
16	20	F	POTS, labile HTN	None	N/A	N/A	N/A	None	No	Yes	No	No	No	Yes	Yes
17	16	F	IST, NCS	None	N/A	N/A	N/A	None	Yes	Yes	Yes	Yes	No	Yes	Yes
18	27	F	IST	None	N/A	N/A	N/A	MV thickening	Yes	Yes	No	No	Celiac disease	No	Yes
19	17	F	POTS	None	N/A	N/A	N/A	None	Yes	Yes	No	Yes	No	Yes	Yes
20	11	F	POTS	None	N/A	N/A	N/A	None	Yes	Yes	Yes	No	No	Yes	N/a
21	38	F	POTS	None	N/A	none	3	None	Yes	Yes	No	No	Thyroiditis	No	Yes
22	24	M	POTS	None	N/A	N/A	N/A	None	No	No	No	No	Thyroiditis	No	No

JHS joint hypermobility syndrome, *EDS* Ehlers-Danlos syndrome, *POTS* postural tachycardia syndrome, *HTN* hypertension, *CRPS* complex regional pain syndrome, *NCS* neurocardiogenic syndrome, *PM* pacemaker, *IST* inappropriate sinus tachycardia, *GI* gastrointestinal, *TPN* total parenteral nutrition, *TF* tube feeds, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *MI* myocardial infarction, *TIA* transient ischemic attack, *N/A* not applicable, *PFO* patent foramen ovale, *MV* mitral valve, *CAPS* catastrophic antiphospholipid syndrome, *AIH* autoimmune hepatitis

[a] Fibromuscular dysplasia and vascular EDS were ruled out

Table 2 Summary of major clinical findings

	All patients ($N = 22$)	JHS/EDS ($N = 7$)	CRPS ($N = 4$)
Mean age at symptom onset	26.5 years (range 6–48)	20.5 years (range 11–38)	26.3 years (range 16–42)
Female	19/22 (86%)	7/7 (100%)	3/4 (75%)
Thrombotic event(s)	13/22 (59%)	2/7 (29%)	4/4 (100%)
Arterial thrombosis	10/22 (45%)	0/7 (0%)* $p = 0.005$	3/4 (75%)
Mean time from onset of autonomic disorder to thrombotic event	4.4 years (range 0–17)	2.25 years (range 1.5–3)	3.5 years (range 0–8)
Fetal loss	5/9 (55.6%)—4/5 in the first trimester	0/1 (0%)	1/1 (100%)
Live birth	8/9 (89%)	1/1 (100%)	0/1 (0%)
Migraine	20/22 (91%)	6/7 (86%)	4/4 (100%)
Memory loss	19/22 (86%)	5/7 (71%)	3/4 (75%)
Livedo reticularis	14/22 (64%)	4/7 (57%)	3/4 (75%)
Raynaud's phenomenon	14/22 (64%)	4/7 (57%)	3/4 (75%)
Other APS manifestations	14/22 (64%)	2/7 (28%)	4/4 (100%)
Other autoimmune disorder	8/22 (36%)—none had lupus	1/7 (14%)	1/4 (25%)
JHS/EDS	7/22 (32%)	7/7 (100%)	1/4 (25%)
Postural tachycardia syndrome	16/22 (73%)	6/7 (86%)	2/4 (50%)
More than one autonomic disorder	10/22 (45%)	4/7 (57%)	3/4 (75%)
Disability	17/19 (89%)	4/5 (80%)	4/4 (100%)
IgM antiphospholipid antibody(s)	21/22 (95%)	7/7 (100%)	3/4 (75%)
Average SGNFD (normal ≥38.2%)	28.8%	27.1%	28.5%
Sensory small fiber neuropathy	15/21 (71%)	7/7 (100%)* $p = 0.02$	4/4 (100%)

JHS joint hypermobility syndrome, *EDS* Ehlers-Danlos syndrome, *CRPS* complex regional pain syndrome, *IgM* immunoglobulin M, *SGNFD* sweat gland nerve fiber density

*Statistically significant when compared to the non-JHS/EDS patients. Statistical analysis was performed using Fisher's exact test and statistical significance was defined as a p value <0.05

Table 3 Autonomic disorders

Postural tachycardia syndrome	16/22 (73%)
Neurocardiogenic syncope	5/22 (23%)
Inappropriate sinus tachycardia	3/22 (14%)
Labile hypertension	5/22 (23%)
Complex regional pain syndrome	4/22 (18%)
Severe gastrointestinal dysmotility[a]	3/22 (14%)
Neurogenic bladder requiring catheterization	2/22 (9%)
More than one disorder	10/22 (45%)

[a] Severe was defined as requiring total parenteral nutrition, tube feedings, and/or colectomy due to toxic megacolon. Less severe gastrointestinal dysmotility was present clinically in the majority of patients

are often normal. Other tests of cardiac autonomic function include heart rate and/or blood pressure responses to the Valsalva maneuver and deep breathing and functional tests of sweating and gastrointestinal motility also exist. None of the latter tests have a high sensitivity, however, and many are only available in specialty centers [17]. Skin biopsy, by contrast, is easy to perform and is emerging as the gold standard to diagnose small fiber sensory and autonomic neuropathies with an estimated sensitivity and specificity of close to 90% [18]. The use of skin biopsy in clinical practice was first reported in 1990 [19]. The technique has since been optimized and normative data for age- and gender-matched controls now exist [15]. While the specimen processing and analysis is highly complex, commercial laboratories including Corinthian Reference Laboratory and Therapath Neuropathology provide testing kits including the proper fixative that facilitates processing of outside samples. Obtaining a pathological diagnosis is helpful in obtaining a trial of immune modulatory therapy in these patients.

We have described 22 patients in which autonomic neuropathy was the initial manifestation of APS. Postural tachycardia syndrome was seen most commonly, but other cardiac autonomic disorders were also seen, as was complex regional pain syndrome, severe gastrointestinal dysmotility, and neurogenic bladder, and 45% of the patients had more than one autonomic disorder. While three patients had severe gastrointestinal dysmotility requiring artificial nutrition or colectomy for toxic megacolon, it should be noted that most of the other patients had symptoms suggestive of less severe gastrointestinal dysmotility, most commonly nausea and early satiety.

Eight of the 22 (36%) patients had symptom onset before age 21 and there are striking similarities between the present patients and those previously reported by Oaklander with "unexplained juvenile-onset small fiber polyneuropathy" [20]. In Oaklander's report, most patients were female, 98% had symptoms suggestive of autonomic dysfunction, severe migraines were common, and there were complex regional pain syndrome features in some. While none were reportedly tested for APS, 89% had immune-related laboratory abnormalities, most commonly a positive ANA and/or low complement levels, both of which are seen commonly in APS, including in many of our patients. As with our patients, most were unable to attend school or work, but 80% improved with immune modulatory therapy. Only sensory (not sweat gland) nerve fiber density was reported in these patients. While the focus of the current report has been autonomic, 71% of our patients did have an associated small fiber sensory neuropathy and this may account for pain seen in some APS patients.

Table 4 Antiphospholipid antibody testing

Patient	aCL IgM	aCL IgG	aCL IgA	aB2GPI IgM	aB2GPI IgG	aB2GPI IgA	LA	aPS IgM	aPS IgG	aPS IgA	aPSPT IgM	aPSPT IgG	aPT IgM	aPT IgG	Total
Positive	**>12**	**>15**	**>12**	**>20**	**>20**	**>20**		**>24**	**>10**	**>19**	**>30**	**>30**	**>19**	**>19**	
1	*17*											***32***			2
2	*16*							***54***				***31***	***36***		4
3			NT			NT	POS	NT	NT	NT	NT	NT	NT	NT	1
4	*27*										***35***				2
5	*26*							***60***			***33***			***23***	4
6	*23*						POS						***21***		3
7			***35***			***>80***				***22***			***36***		4
8	*17*							***32***			***40***				3
9	*20*							***36***							2
10	*18*		NT			NT		***25***		NT	NT	NT	NT	NT	2
11	*13*								***13***			***31***			3
12	*14*								***14***						2
13	*17*				*22*								***24***		3
14	*22*							***58***							2
15	*14*											***46***			2
16	*19*										***42***		***25***		3
17	*21*	*22*							***30***						3
18	*15*											***30***			2
19	*17*							***28***							2
20	*14*										***45***		***20***		3
21	*14*												***28***		2
22	*14*													***35***	2

The "traditional" antiphospholipid antibodies included in the Sapporo classification criteria are shown in italics and the "secondary" prothrombin-associated antibodies are shown in bold italics. The positive cut-off value is shown in bold below each antibody name. All antibody results are reported in units. All patients were tested on two or more occasions at least 12 weeks apart; the highest titer for each antibody type is reported. All ELISA testing was performed using INOVA assays, except for the antiprothrombin IgG and IgM testing which was performed by ARUP

IgM immunoglobulin M, *IgG* immunoglobulin G, *IgA* immunoglobulin A, *aCL* anticardiolipin, *aB2GPI* = antibeta-2 glycoprotein I, *LA* lupus anticoagulant, *aPS* antiphosphatidylserine, *aPSPT* antiphosphatidylserine-prothrombin, *aPT* antiprothrombin, *POS* positive, *NT* not tested

Sensory neuropathy was seen most commonly in our patients with joint hypermobility and complex regional pain syndrome, occurring in 100% of each of these patients, but in only four of the 10 (40%) patients without these conditions.

Complex regional pain syndrome and joint hypermobility deserve special mention. Complex regional pain syndrome is a pain disorder associated with the highest possible level of pain on the 50-point McGill pain scale that was designed to stratify the most painful conditions, scoring higher than childbirth and amputation without anesthesia and cancer pain [21]. In addition to pain, there is evidence for autonomic dysregulation with color and temperature changes and sweating abnormalities in the affected limb. Small numbers of patients prevented statistically significant differences to be determined, but for the four patients with complex regional pain syndrome in the present study, it was the initial manifestation of APS in all and each went on to develop multiple other severe manifestations, including thrombosis and other APS manifestations, and three of the four had more than one autonomic disorder. It should also be noted that two of the four patients developed complex regional pain syndrome in a limb affected by arterial or venous thrombosis as did the patient previously reported by Tsutsumi et al. [5]. Lack of awareness of this association may lead to a misdiagnosis of complex regional pain syndrome and/or thrombosis.

We again noted a significant number of patients with joint hypermobility syndrome (7 of 22) consistent with the known association between autonomic disorders and joint hypermobility syndrome [22]. As shown in Tables 1 and 2, the patients with joint hypermobility had a trend toward less severe presentations with a statistically significant lower arterial thrombotic risk as well as a trend toward a lower risk for other APS manifestations. These patients, however, presented with autonomic dysfunction at a younger age on average than those without joint hypermobility. Since connective tissue disorders predispose to cardiac autonomic dysfunction, the two-hit

Table 5 Skin biopsy results

Patient	# sites biopsied	Sensory ENFD	Autonomic mean SGNFD(%)[a] (normal > =38.2%)
1	2	Reduced, uncertain (only lower legs done)	30.3
2	3	Reduced, LD	27.2
3	3	Reduced, NLD	28.6
4	4	Reduced, LD	28.2
5	3	Reduced, NLD	33.7
6	2	Reduced, NLD	31.6
7	2	Normal	19.4
8	3	Normal	27.5
9	2	Normal	28.8
10	Not done	Not done	Not done
11	3	Reduced, NLD	29.1
12	2	Reduced, LD	35.3
13	3	Reduced, NLD	32.6
14	3	Reduced, LD	31.1
15	3	Normal	29.9
16	3	Reduced, LD	18.5
17	3	Reduced, NLD	26.3
18	3	Normal	33.7
19	3	Normal	20.7
20	3	Reduced, NLD	33.1
21	3	Reduced, LD	31.2
22	2	Reduced, NLD	28.6
Total	*Mean 2.8*	*Reduced in 15/21 (71%)*	*Mean 28.8*

ENFD epidermal nerve fiber density (sensory), *SGNFD* sweat gland nerve fiber density (autonomic), *LD* length dependent, *NLD* nonlength dependent

[a] For all patients tested, the SGNFD was abnormal at all sites biopsied; this value represents the median SGNFD percentage of all sites biopsied

hypothesis may result in these patients presenting clinically with dysautonomia, despite less severe APS.

Several patients had labile hypertension without underlying renal artery stenosis or pheochromocytoma. This was reported in early descriptions of APS [4] in association with livedo reticularis and is likely due to dysregulation of the autonomic nervous system in these patients [23]. Labile hypertension is important to recognize in APS as hypertension and other traditional vascular risk factors act synergistically with antiphospholipid antibodies to increase thrombotic risk, presumably as all can cause endothelial dysfunction [24, 25]. This risk may be increased with significant lability of blood pressure, which would be expected to induce greater alterations in laminar blood flow and therefore greater endothelial activation. It is possible that widely fluctuating heart rates seen in most patients with autonomic dysfunction might also increase thrombotic risk by a similar mechanism. Supportive of this hypothesis is that patient 8 had multivessel cerebral artery dissection and stroke without evidence for fibromuscular dysplasia or vascular Ehlers-Danlos syndrome and spontaneous arterial dissection in APS has been previously reported in several publications [26, 27]. Thirteen of 22 (59%) of our patients had a thrombotic event and some had more than one, despite most having low-titer IgM antibodies. The timing of the thrombotic events varied greatly from concomitant with the autonomic disorder in one patient with complex regional pain syndrome to 17 years later, with a median of 4 years after the onset of symptomatic autonomic dysfunction. There was a statistically significant lower arterial thrombotic risk in the patients with joint hypermobility and a trend toward a higher risk in patients with complex regional pain syndrome.

The diagnosis of APS in a patient with an autonomic disorder provides a window of opportunity to prevent thrombosis. This may be done by careful management of the autonomic disorder with agents that improve autonomic tone and reduce wide blood pressure and heart rate fluctuations. It might also be done by avoiding smoking and exogenous estrogen and with strict attention to secondary vascular risk factors. A trial of antiplatelet agents and/or anticoagulants in patients with clinical manifestations of APS that may be responsive to these agents, such as

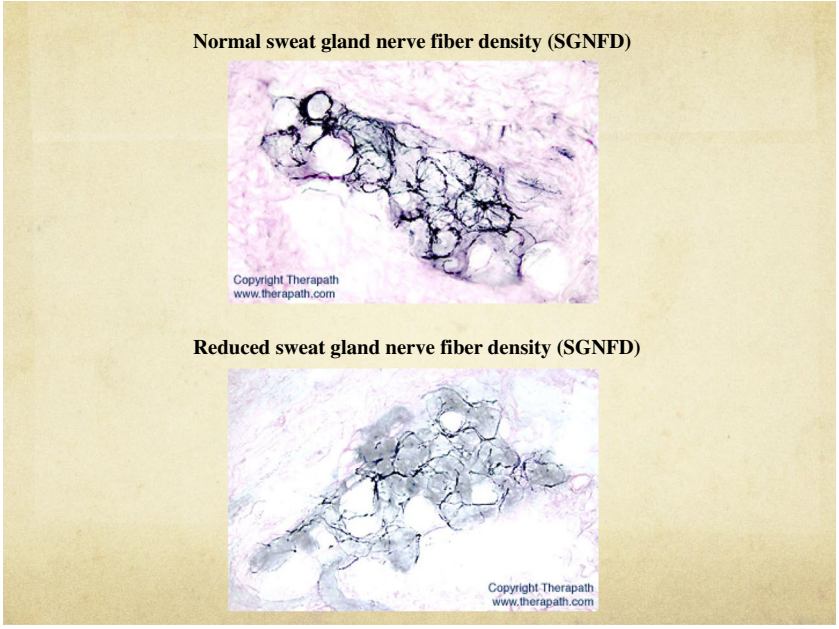

Fig. 1 Illustrative skin biopsy photographs demonstrating normal and reduced sweat gland nerve fiber density, provided with kind permission by Therapath Neuropathology

migraine, memory loss, or stress fractures [28, 29], might also be considered.

Similar to our initial publication, we found that migraine was present in most patients, often with aura and/or status migrainosus. Memory loss was also usually present and should be distinguished from "brainfog" (difficulty concentrating), which is present in most patients with dysautonomia of any cause due to cerebral hypoperfusion. Patients with dysautonomia due to APS typically describe not only brainfog but also "blank spells" in their thinking, such as being unable to recall their own phone number. Word-finding difficulty is also common in these patients. It has been previously demonstrated that severe migraine in APS may be followed some years later by stroke [30] and a trial of antiplatelet therapy and/or anticoagulation therapy as previously described [31] might be considered in the patients with migraine and/or memory loss. A definitive response suggests a microthrombotic or "sludging" pathogenesis, which is supported by animal models [32] and human autopsy data [33, 34], and may identify a subset of patients at an increased risk for thrombosis. While there was an important risk of thrombosis in the present patients, significant pregnancy morbidity was minimal. Interestingly, unexplained and recurrent stress fractures were seen in three of the patients. Like migraine and memory loss, stress fractures in APS might also occur by a microthrombotic mechanism. In addition, bone is densely innervated by small fiber neurons and small fiber neuropathy can cause osteoporosis (as is seen in complex regional pain syndrome), bone pain, and pathological fractures [35].

Given the suspicion as noted above that migraine and memory loss may occur due to microthrombosis or vascular "sludging" in this context, it is tempting to speculate that the autonomic neuropathy might as well. The small fiber nerves that comprise the peripheral autonomic nervous system are perfused by the smallest of blood vessels—5 to 10 μm in diameter, similar in size to the diameter of a red blood cell (7 μm). It is interesting to note that all patients except one in the present study had IgM antibodies. Pentameric IgM molecules might be more likely to cause vascular "sludging" due to hyperviscosity than monomeric IgG antibodies. An alternative hypothesis regarding the pathogenesis of the autonomic neuropathy is that the antiphospholipid antibodies might bind small fiber neurons directly and alter their function as has been demonstrated with other neuronal types [2, 3, 36]. The latter hypothesis is supported by anecdotal improvement noted in a number of patients with autonomic neuropathy due to APS treated with intravenous immunoglobulin. These mechanisms are not mutually exclusive and either or both might occur in any given patient as different antibody profiles could result in differential clinical manifestations and pathogenic mechanisms.

Table 4 illustrates the importance of the prothrombin-based antiphospholipid antibodies in this population; all patients described in the present report tested for the newer antibodies had at least two different antibodies detected. If only traditional antibodies were used, the low-titer anticardiolipin IgM antibodies present alone might have been discounted but, as shown, they may correlate with significant clinical manifestations.

The association of APS and autonomic neuropathy highlights the emerging importance of autoimmunity in autonomic nervous system disease [9, 37]. We have shown that autonomic neuropathy may be the initial manifestation of APS as has been shown previously for Sjogren's syndrome [38], chronic inflammatory demyelinating polyneuropathy [39], and

multiple sclerosis [40]. Similarly, it has recently been reported that dysautonomia may precede the development of rheumatoid arthritis and it has been suggested that autonomic dysfunction may play a role in the etiopathogenesis of rheumatoid arthritis [41]. The emerging understanding of the interaction between the autonomic nervous system and the immune system might explain why a large number of autoimmune disorders have been reported in association with autonomic dysfunction [42, 43]. The limitations of the current study include its retrospective design and single-center nature as well as the relatively small number of patients. Further studies into this association are warranted.

Conclusion

APS is best known for causing thrombosis and pregnancy morbidity but, like other systemic autoimmune diseases, it may have wide-ranging clinical manifestations. Indeed, it has been described as a "neurological disease" [44]. We have demonstrated that autonomic neuropathy—in its many guises—may occur in association with APS and that it may be the presenting manifestation of the syndrome. Increased awareness of this association is important, as it is associated with a high degree of disability and an important thrombotic risk, despite usually low-titer IgM antibodies. In addition, anecdotal experience has shown that antithrombotic and immune modulatory therapy with intravenous immunoglobulin may result in meaningful clinical improvement in this context.

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