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CONCISE REPORT

Postural tachycardia syndrome (POTS) and other autonomic disorders in antiphospholipid (Hughes) syndrome (APS)

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Background: Antiphospholipid syndrome (APS) is an autoimmune hypercoagulable disorder that has been shown to cause a large number of cardiac and neurological manifestations. Two recent studies have demonstrated abnormalities in cardiovascular autonomic function testing in APS patients without other cardiovascular or autoimmune disease. However, an association between autonomic disorders such as postural tachycardia syndrome and APS has not previously been described. **Methods and results:** Data were obtained by retrospective chart review. We identified 15 patients who have been diagnosed with APS and an autonomic disorder. The median age of the patients at the time of data analysis was 39 years. The autonomic disorders seen in these patients included postural tachycardia syndrome, neurocardiogenic syncope and orthostatic hypotension. The majority of patients (14/15) were female and the majority (14/15) had non-thrombotic neurological manifestations of APS, most commonly migraine, memory loss and balance disorder. Many also had livedo reticularis (11/15) and Raynaud's phenomenon (nine of 15). In some patients, the autonomic manifestations improved with anticoagulation and/or anti-platelet therapy; in others they did not. Two patients with postural tachycardia syndrome who failed to improve with the usual treatment of APS have been treated with intravenous immunoglobulin with significant improvement in their autonomic symptoms. **Conclusion:** We believe that autonomic disorders in APS may represent an important clinical association with significant implications for treatment. *Lupus* (2014) **0,** 1–6.

Key words: Hughes syndrome; antiphospholipid syndrome (APS); postural tachycardia syndrome (POTS); neurocardiogenic syncope (NCS); autonomic disorders; intravenous immunoglobulin (IVIG)

Introduction

Antiphospholipid (Hughes) syndrome (APS) is a hypercoagulable autoimmune disorder associated with antiphospholipid antibodies that causes both arterial and venous thrombosis as well as pregnancy morbidity. Non-thrombotic manifestations also occur in APS and include valvular heart disease,[1–4] cardiac syndrome X,[5] focal arterial stenosis,[6] cardiomyopathy,[1–3] nephropathy,[7] stress fractures,[8] thrombocytopenia,[9] hemolytic anemia,[9] livedo reticularis,[10] skin ulcers and necrosis,[10] as well as a large number of neurological manifestations.[11] Labile hypertension without associated renal disease and autonomic neuropathy were reported in early descriptions of the syndrome,[12] and a recent study by Bilora et al. demonstrated abnormalities in cardiovascular autonomic function testing in APS patients without cardiovascular disease, cardiovascular risk factors or other autoimmune disorders.[13] Garcia et al. also recently reported impaired aerobic exercise capacity and cardiac autonomic control in APS patients.[14] However, an association between APS and autonomic disorders, such as postural tachycardia syndrome (POTS), neurocardiogenic syncope (NCS) and neurogenic orthostatic hypotension (OH), has not previously been reported. We describe a series of 15 patients with APS and a disorder of the

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autonomic nervous system and propose an association between the two.

Methods

This is a retrospective chart review of 15 patients who have been diagnosed with APS as well as POTS, NCS, and/or OH. Patients were personally examined and followed by one or the other of the authors.

The diagnosis of APS was determined by the presence of at least one antiphospholipid antibody (lupus anticoagulant, anticardiolipin immunoglobulin IgG or IgM, or beta 2 microglobulin I IgG or IgM) on more than one occasion at least 12 weeks apart as well as one or more clinical manifestations of the syndrome. Not all patients met the revised Sapporo classification criteria for definite APS, which requires thrombosis or specific pregnancy morbidity and medium to high titer antibody levels.[15] The classification criteria were designed for rigorous clinical research studies not for diagnosis, and patients with low titer antibody positivity were included as were patients without a history of thrombosis who had well-described non-thrombotic manifestations of the syndrome.

All patients in the present study underwent formal tilt table testing. POTS was diagnosed as previously described based on the presence of clinical features of orthostatic intolerance and an increase in heart rate of at least 30 beats per minute within 10 minutes of tilt table testing without evidence of OH.[16,17] Other autonomic tests including deep breathing, the Valsalva maneuver, the handgrip test and the quantitative sudomotor axon reflex test (QSART) may provide additional information and allow better characterization of the autonomic disorder. These tests were performed in several but not all of the patients included in the present study. NCS, also known as neurally mediated syncope or vasovagal 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.[17] OH was diagnosed if there was a reduction in systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg within three minutes of the tilt table test.[17]

Results

We identified 15 patients with APS and a disorder of the autonomic nervous system. The clinical characteristics of the patients are shown in Table 1 and the frequency of their APS manifestations is shown in Table 2. The median age at the time of data collection was 39 years and ranged from 15 to 66 years. However, the age at the time of diagnosis of APS and/or the autonomic disorder occurred at least a few years earlier in most of the patients and dated back to childhood (as early as age 12) in some. The dates of diagnosis were not available for all patients and the details of the timing of the onset of the APS symptoms relative to the autonomic symptoms were not available for many of the patients, but for some the symptoms began concomitantly. Eight of the 15 patients had POTS, eight had NCS (two of these required pacemaker placement), three had OH, one had inappropriate sinus tachycardia (IST) and one had complex regional pain syndrome type I (CRPD, formerly known as reflex sympathetic dystrophy, RSD), which has previously been described in association with APS.[18] Six of the 15 patients had more than one autonomic disorder. Fourteen of the 15 patients were female and 14/15 had non-thrombotic neurological manifestations of APS, which included most commonly migraine, memory loss and imbalance. The majority (11/15) of patients had livedo reticularis and nine of 15 had Raynaud's phenomenon. Eight of the patients had at least one other autoimmune disorder and three of 15 had joint hypermobility syndrome (JHS). One patient (#13) developed APS, POTS and NCS two months after human papillomavirus (HPV) vaccination, and four patients had a family history of APS. Most (11/15) of the patients required treatment with anticoagulation and three required both anticoagulation and an anti-platelet agent for optimal APS symptom control. Two patients have not yet been treated. We did not find any pattern in terms of the titer or type of the antiphospholipid antibodies present. There was a high degree of disability noted in these relatively young patients.

Discussion

APS is an autoimmune hypercoagulable disorder best known for its tendency to cause thrombosis—arterial, venous and placental. However, APS is a multisystem disorder[19] and in the original description of the syndrome by Hughes in 1983, cerebral involvement was felt to play a central role.[20] Indeed, since then, APS has been found to cause wide-ranging neurological manifestations,

Table 1 Clinical Characteristics of the Patients

Patient	*Age*	*Gender*	*APS Manifestations*	*APS Treatment*	*Autonomic Disorder*	*Comorbid Illness(es)*
1	45	F	MC, TIA, migraine, memory loss, imbalance, livedo	LMW heparin, aspirin	OH	adult Stills, JRA
2	46	F	MC, hemiplegic migraine, livedo, transverse myelitis, trigeminal neuralgia	LMW heparin	NCS, OH	none
3	45	F	TIA, migraine, memory loss, imbalance, livedo, Raynaud's, stress fracture	LMW heparin, clopidogrel IVIG	POTS	none
4	56	F	TIA, migraine, memory loss, imbalance, livedo, Raynaud's	LMW heparin	POTS	SLE, UC, AS, JHS
5	39	F	TIA, migraine, Guillain-Barré syndrome	warfarin	NCS, CRPD	AS, JHS
6	66	F	MC, migraine, memory loss, imbalance, livedo	clopidogrel	OH	none
7	37	F	MC, TIA, migraine, memory loss, livedo, Raynaud's, imbalance, sinus venous thrombosis	warfarin	POTS, IST	JHS
8	37	F	MC, migraine, imbalance, Raynauds, renal artery stenosis	LMW heparin, aspirin	POTS, NCS	Crohn's, seronegative arthritis
9	38	F	migraine, memory loss, imbalance, livedo, Raynaud's, PE, thrombocytopenia	warfarin	NCS (PM)	SLE, Sjogren's
10	37	M	recurrent PE	warfarin	POTS, NCS (PM)	none
11	40	F	migraine, livedo, Raynaud's	aspirin	NCS	RA, Hashimoto's thyroiditis
12	32	F	migraine	none	POTS	none
13	15	F	migraine, memory loss, imbalance, livedo, Raynaud's	none	POTS, NCS	UCTD
14	29	F	DVT/PE, memory loss, livedo, Raynaud's, peripheral neuropathy	Warfarin, IVIG	POTS	none
15	47	F	DVT, MC, migraine, memory loss, imbalance, livedo, Raynaud's, stress fractures	aspirin (previously warfarin)	NCS	Celiac disease

Abbreviations: MC: miscarriage, TIA: transient ischemic attack, PE: pulmonary embolus, DVT: deep vein thrombosis, LMW: low molecular weight (heparin), IVIG: intravenous immunoglobulin, OH: orthostatic hypotension, NCS: neurocardiogenic syncope, POTS: postural tachycardia syndrome, PM: pacemaker, CRPD: complex regional pain disorder, IST: inappropriate sinus tachycardia, JRA: juvenile rheumatoid arthritis, SLE: systemic lupus erythematosis, UC: ulcerative colitis, AS: ankylosing spondylitis, JHS: joint hypermobility syndrome, RA: rheumatoid arthritis, UCTD: undifferentiated connective tissue disease.

Table 2 Frequency of APS Manifestations

Migraine	13/15 = 87%
Livedo reticularis	11/15 = 73%
Memory loss	9/15 = 60%
Imbalance	9/15 = 60%
Raynaud's phenomenon	9/15 = 60%
Miscarriage	6/13 = 46%
Transient ischemic attack	4/15 = 27%
Venous thromboembolism	4/15 = 27%
Stress fractures	2/15 = 13%
Thrombocytopenia	1/15 = 7%
Renal artery stenosis	1/15 = 7%
Venous sinus thrombosis	1/15 = 7%
Transverse myelitis	1/15 = 7%
Guillain-Barré syndrome	1/15 = 7%
Trigeminal neuralgia	1/15 = 7%
Peripheral neuropathy	1/15 = 7%

including stroke, memory loss, migraine, seizures, balance disorder, chorea, Guillain-Barré syndrome, multiple sclerosis-like syndrome, transverse myelitis, sleep disorder and trigeminal and peripheral neuropathy.[11,21] APS is also associated with an increased risk of cardiovascular disease and mortality.[1–6,13,14] The cardiac and neurological manifestations seen in APS occur because of both thrombotic and non-thrombotic mechanisms. The pathogenesis of the non-thrombotic manifestations seen in APS is complex and incompletely understood, but includes antibody-mediated activation of endothelial cells, platelets, monocytes, clotting factors and complement pathways.[2,22] It has also been shown that antiphospholipid antibodies can bind glial cells, myelin and neurons and alter their function.[11,23]

POTS, NCS and OH are disorders of the autonomic nervous system that cause abnormalities in cardiovascular autonomic regulation. POTS occurs most commonly in women of reproductive age and can be as disabling as congestive heart failure and chronic obstructive pulmonary disease.[24] Manifestations of POTS include features of cerebral hypoperfusion such as dizziness, pre-syncope, syncope, nausea, vomiting, headache and mental clouding, as well as features of sympathetic overactivation such as tremulousness, palpitations, chest pain, shortness of breath and orthostatic tachycardia. Other common symptoms include fatigue, sleep disturbance and heat and exercise intolerance.[16,25] The pathophysiology of POTS includes disturbances in blood volume regulation leading to chronic hypovolemia, denervation of the sympathetic nerve fibers from the lower extremities, elevated levels of plasma norepinephrine and mast cell activation.[16] POTS is a heterogeneous disorder that may occur following viral infection, pregnancy, trauma[26] or vaccination;[27] it may also occur in association with mast cell activation disorder,[28] Lyme disease,[29] JHS[30] or autoimmune disease.[31] NCS is also a heterogeneous disorder. It occurs when there is a relatively sudden change in autonomic nervous system activity leading to a fall in blood pressure, heart rate and cerebral perfusion. It is typically preceded by prodromal symptoms and signs, such as pallor, diaphoresis, nausea, abdominal discomfort, yawning and hyperventilation. During NCS, there is a decrease in efferent sympathetic vasoconstrictor nerve activity leading to a loss in vasoconstrictor tone and an increase in parasympathetic (vagal) outflow. This in turn results in bradycardia, the degree of which varies widely from a small reduction in peak heart rate to several seconds of asystole.[17] Like POTS, NCS can also be very disabling as some patients experience syncopal episodes on a daily basis. OH is caused by an excessive fall in cardiac output or by defective or inadequate vasoconstrictor mechanisms.[17] When OH is caused by an inadequate release of norepinephrine from sympathetic vasomotor neurons leading to vasoconstrictor failure, the term ''neurogenic'' OH is used and this applies to the OH seen in the patients in our study.

Because they are associated with protean manifestations and there are a limited number of physicians with expertise in the autonomic nervous system, autonomic disorders have historically frequently either gone undiagnosed or have been misdiagnosed as chronic fatigue syndrome, anxiety or depression. The past decade, however, has seen an explosion of knowledge about the autonomic nervous system and the number of medical centers offering formal autonomic testing, and evaluation has increased significantly. With increasing awareness and diagnosis, one of us (GH) has noted an apparent association between various autonomic disorders and APS. This is not surprising since APS has been associated with multiple other neurological manifestations.

We have described a series of 15 patients with APS and a disorder of the autonomic nervous system. The autonomic disorders seen in these patients included most commonly POTS and NCS, but OH, IST and CRPD were also noted and six of the 15 patients had more than one autonomic disorder. All but one of the patients were female and all but one had non-thrombotic neurological manifestations of APS, most frequently migraine, memory loss and imbalance. Livedo reticularis and Raynaud's phenomenon were also noted in many of the patients. Three of the patients had another autoimmune disorder (systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and/or Sjögren's syndrome) that has previously been shown to be associated with autonomic nervous system dysfunction.[31] Many of the neurological manifestations found in SLE, however, have over the years been shown to be more related to APS than to SLE.[20,32,33] Antiphospholipid antibodies are present in 25%–50% of patients with RA, Sjögren's syndrome and SLE, and we hypothesize that the autonomic dysfunction in patients with these disorders may be associated with the presence of antiphospholipid antibodies and/or other antibodies targeting the autonomic ganglia, cardiac proteins or vascular adrenergic or muscarinic receptors, all of which have been identified in subsets of patients with POTS.[24,34–36] Clearly, however, the presence of autonomic nervous system dysfunction in autoimmune disease is complex and the mechanisms involved are incompletely understood.

Lastly, one patient in our series (#13) developed POTS, NCS, APS and positive antinuclear antibodies (ANA) two months after HPV vaccination. Six other patients who developed POTS after HPV vaccination have been reported recently by Blitshteyn.[27] In the latter case series, the antiphospholipid antibody status is unknown, but two patients tested positive for ANA. These case reports further advance autoimmunity as an underlying mechanism of POTS as it relates both to vaccination and to APS.

We recognize there is a referral bias in the patients included in our case series, and we do not know what the frequency of autonomic

dysfunction may be in the overall APS patient population, nor how often antiphospholipid antibodies may be present in patients with various autonomic disorders. APS is estimated to affect approximately 1% of the population and symptoms such as severe fatigue and brain fog that could be explained by autonomic dysfunction are not uncommon, so this may turn out to be an important association. In addition, the present study highlights the fact that many autoimmune and vasomotor disorders predisposing to autonomic dysfunction may overlap and coexist in the same patient, requiring recognition and tailored strategies for management. Thus, our findings suggest that patients with APS and autonomic symptoms should be tested for an autonomic disorder with a tilt table test and, if available, complete autonomic function testing. In addition, these findings suggest that patients with autonomic dysfunction and clinical features suggestive of APS should be tested for antiphospholipid antibodies. A correct diagnosis both of APS and autonomic disorders has important therapeutic implications as proper management of both conditions can result in significant clinical improvement.

There are multiple therapies that may benefit patients with autonomic disorders, including graded exercise programs, a high-sodium diet, fludrocortisone, midodrine, beta blockers, central sympatholytics and several other pharmacological treatments. It is well known that thrombotic complications of APS are treated with anticoagulation. Less well known, however, is that many non-thrombotic manifestations of APS often improve significantly or may even be completely aborted with anti-platelet agents and/or anticoagulation.[11,21,37] This includes migraine (which is often severe and refractory to standard treatment), memory loss, imbalance, chorea, seizure disorder, multiple sclerosis-like syndrome, myelopathy, cardiac syndrome X, stress fractures, avascular necrosis, livedo reticularis and Raynaud's phenomenon. Because this response is often rapid (e.g. less than 24 hours), even for symptoms present for years, we hypothesize that these manifestations may occur because of "sludging" of the blood[21] caused by interactions of the antiphospholipid antibodies with platelets, clotting factors and/or endothelial cells. Anecdotally, meaningful improvement in autonomic symptoms with the proper anticoagulation and/or anti-platelet therapy has also been noted in some (but not all) APS patients by one of the authors (GH). Finally, intravenous Ig (IVIG) use has been shown to be beneficial in some patients with autonomic dysfunction due to autoimmune autonomic ganglionopathy,[36] small fiber neuropathy,[38] multisystem atrophy[39] and, anecdotally, in some patients with POTS secondary to an underlying autoimmune disease. Additionally, IVIG is used to treat certain manifestations of APS, including thrombocytopenia and refractory recurrent fetal loss and it is also used in the treatment of catastrophic APS.[40,41] There is also increasing evidence that rituximab is effective in treating select patients with APS manifestations not responsive to treatment with antiplatelet agents and/or anticoagulation.[42] Two patients (#3, #14) in the present study with POTS who did not improve with standard APS treatment (despite a response of many of the APS manifestations) have been treated with IVIG with significant improvement in their autonomic symptoms. One of these patients has had a decrease in factor VIII activity (a marker of endothelial activation) from 289% prior to starting IVIG to 133% after six months of treatment (normal 50%–150%).

In summary, we have described 15 patients with APS and autonomic nervous system dysfunction. Our case series highlights the complexity of autonomic involvement in autoimmune disease, and we believe this clinical association may have important implications for the management both of autonomic disorders and APS.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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