Peripheral neuropathy in antiphospholipid syndrome: a systematic review

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Summary

Objective. Antiphospholipid syndrome (APS) is a disease characterized by recurrent thrombosis in the presence of antiphospholipid antibodies. The most uncommon events described in the literature have been peripheral neurological disorders. This paper aims to systematically review the cases of peripheral neuropathy (PN) in APS patients.

Methods. We systematically searched articles on PN and APS with English abstracts in PubMed from 1966 to August 2022.

Results. We found 10 articles on PN and APS with 100 patients. Age varied from 25 to 78 years; 86-100% of patients in these studies were female. Most patients had primary APS (n=9); one article considered secondary APS associated with other autoimmune diseases. Disease duration varied from 0 to 8.6 years, but three articles did not provide this information. Most studies showed positivity for anticardiolipin antibodies (n=5), followed by lupus anticoagulant (n=2).

Regarding clinical NP features, mononeuritis multiplex (n=3) and autonomic neuropathy (n=3) were more common than peripheral polyneuropathy (n=2). Nerve biopsy was performed in 7 articles and resulted positive in all cases. Concerning treatment, most articles used anticoagulation (n=4), followed by glucocorticoids (n=3), intravenous immunoglobulin, and immunosuppressive drugs (n=1). Most cases improved after treatment (n=7).

Conclusions. This study demonstrates that PN is a rare complication in APS and occurs more frequently in females, associated with antiphospholipid antibody positivity. Most cases were confirmed by electroneurography or nerve biopsy and had a good outcome.

Introduction

Antiphospholipid syndrome (APS) is an acquired thrombophilia characterized by thrombosis and/or obstetric events in the presence of persistent antiphospholipid antibodies (aPL) (1). It is pathogenically mediated by antibodies targeting phospholipid-binding proteins, mainly β-2-glycoprotein I (2).

The most common manifestations are thrombotic events such as deep venous thrombosis and stroke. Additional disease presentations include limb ischemia, myocardial infarction, and pulmonary thromboembolism. The clinical spectrum of APS can also include nonvascular manifestations such as thrombocytopenia, livedo reticularis, migraine, and seizures, to name some. Microvascular thrombosis is also part of the APS and includes obstetrical events, kidney lesions, and catastrophic APS. The neurological system, mainly the central nervous system, is involved in 1 to 20% of APS cases (3). Also, some peripheral neurological disorders have been described, although uncommonly (4).

Recently, a new classification for APS was developed and published by the American College of Rheumatology and the European Alliance of Rheumatologic Associations (5). The main novelty introduced by this set of criteria consists in the identification of six clinical domains (macrovascular venous thromboembolism, macrovascular arterial thrombosis, microvascular, obstetric, cardiac valve, and hematologic) and two laboratory domains (lupus anticoagulant functional coagulation assays, and solid-phase enzyme-linked immunosorbent assays for IgG/IgM anticardiolipin and/or IgG/IgM anti-β2-glycoprotein I antibodies) (5).

This article aims to perform a systematic review of peripheral neuropathy (PN) in APS patients.

Methods

Literature review

We have systematically studied articles published in PubMed/MEDLINE, Web of Sciences, LILACS, and SciELO from 1966 to August 2022 using the following MeSH entry terms: "peripheral neuropathy" and "antiphospholipid syndrome", without language restriction. The reference lists of the selected articles were analyzed to identify other publications. Initially, the three authors (JFC, CAMC, and RRES) independently performed the literature search and independently selected the study abstracts. In the second stage, the same reviewers independently read the full-text articles selected by the abstracts. The third reviewer also resolved disagreements during a consensus meeting. The authors followed the PRISMA guidelines (6). We designed a standardized form to extract the following information from relevant articles regarding the authors and year of publication, the number of patients studied, demographic data, disease duration, nerve biopsy, electroneuromyography features, treatments, and outcomes.

Table 1. Summary of the studies on antiphospholipid syndrome and peripheral neuropathy.

Author, year	Study design	N, female sex	Age, years	Primary or secondary APS	Disease duration	APS clinical manifestations	aPL antibodies	PN alterations	ENMG	Nerve biopsy	Treatment	Outcome
Schofield, 2017 (7)	Retrospective	22, 86%	26.5 (6-48)	Primary	4.4 years	59% thrombotic events	IgM aCL 95%	Autonomic neuropathy (POTS, NCS)	ND	Autonomic neuropathy by skin biopsy	ND	ND
Giorli *et al*., 2016 (8)	Case report	1, 100%	54	Primary	ND	ND	ND	Weakness in distal muscles in all limbs and reduced tendon stretch reflexes in the lower limbs without sensory deficits	Moderately severe polyneuropathy	Mild inflammatory demyelinating neuropathy	High dose GC and IVIg-no response; plasmapheresis and azathioprine; neurostimulation	Improved muscle strength
Takahashi *et al*., 2015 (9)	Autopsy case report	1, male	78	Primary	ND	Livedo, purpura	ND	Mononeuritis multiplex	ND	Axonal degeneration and thrombi on arterioles and venules, without inflammation	Anticoagulation	He improved in PN. But, 2 months later died from venous embolism and infection
Schofield *et al*., 2014 (10)	Retrospective	15, 93%	39 (15-66)	Primary and secondary (SLE 2, Sjögren 1, RA 1, Crohn 1, celiac disease 1)		Livedo, Raynaud phenomenon,	ND	Postural tachycardia syndrome (N=8), neurocardiogenic syncope (n=8), and orthostatic hypotension	ND	Positive skin biopsy	ND	Improved
Etemadifar *et al*., 2013 (11)	Retrospective	1/103, 87%	36.3 ±11.4	Primary	ND	DVT, PTE	ND	ND	ND	ND	ND	ND
Bilora *et al*., 2012 (12)	Case-control	31 APS, 31 controls	47.4 ±21	Primary	ND	ND	ND	ND	ND	ND	ND	ND
Santos *et al*., 2010 (4)	Cross-sectional	26, 92%	38.6 ±8.5	Primary	8.6 ± 3	Arterial: 59%; Venous: 50%; Obstetric:41%	LA: 41%; IgG aCL: 86%; IgM aCL: 55%	Mononeuritis multiplex	41% altered	ND	ND	ND
Rodrigues *et al*., 2010 (13)	Case report	1, 100%	25	Primary	0	Cyanosis of the lower limbs, livedo, malleolar ulcers.	54 GPL, 28 MPL, LA	Pain and partial loss of flexion and extension of the right ankle	Marked degeneration of motor and sensory nere fibers of the posterior tibial and fibular nerves, sensorial of the sural compatible with moneurite multiplex.	Fibrin thrombus of the vasa nervosum, without inflammation	Methylprednisolone pulse therapy and anticoagulation	Improved, complete recovery in 11 months
Jeruc *et al*., 2006 (14)	Case report	1, 100%	49	Primary	ND	Abortion, Raynaud's phenomenon	IgG aCL	Multiple mononeuropathy	ND	Active necrotizing arteritis of the epineural arteries with transmural inflammatory infiltrate and thrombosis	Methylprednisolone 48mg *per ors*	Improved
Erten *et al*., 2004 (15)	Case report	1, 100%	34	Primary	ND	CAPS (heart failure, stroke, cerebral venous thrombosis, multiple cranial and abdominal thromboses)	aCL 27GPL	Peripheral polyneuropathy	Mononeuropathy multiplex with severe axonal degeneration	Severe axonal degeneration with perivascular inflammation related to wallerian degeneration caused by ischemia.	Anticoagulation	Improved. Complete recovery.

aCL, anticardiolipin; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; CAPS, catastrophic antiphospholipid syndrome; ENMG, electroneuromyography; GC, glucocorticoid; IVIg, intravenous immunoglobulin; LA, lupus anticoagulant; N, number; ND, not described; PN, peripheral neuropathy; POTS, postural orthostatic tachycardia syndrome; NCS, neurocardiogenic syncope.

Results

We found 10 articles on APS and PN, totaling 100 patients. Table 1 summarizes these studies (4, 7-15). Most of them were case reports (n=5), with retrospective (n=3), case-control (n=1), and cross-sectional (n=1) studies. Patients were mainly female (86-100% of the study cohort across different studies), and their ages varied from 25 to 78 years. Nine studies included patients with primary APS, and one study recruited patients with secondary APS. Disease duration ranged from 0 to 8.6 years, although most papers did not provide this detail. References 7 and 10 from the same author reported 15 patients in 2014 and 22 in 2017; it is not clear if there is an overlap between these patients.

Most studies showed positivity for anticardiolipin antibodies IgG (25/51, 50%) and IgM (35/51, 67%), followed by lupus anticoagulant (10/51, 20%), whereas three studies (n=49 patients) did not fully characterize the aPL profile.

Clinical PN features included autonomic neuropathy (30/43, 69%), mononeuritis multiplex (3/43, 7%), simplex mononeuropathy (1/43, 2%), and peripheral polyneuropathy (2/43, n=2, 5%).

Nerve biopsy was performed in seven articles and found histologic abnormalities suggestive of PN in all cases.

Only five articles described the treatment for the PN, and all of them were single-case reports: most patients used anticoagulation (n=3), glucocorticoids (n=3), intravenous immunoglobulins, and immunosuppressive drugs (n=1). All the patients improved after treatment, but the outcome was not described in three articles.

Discussion

This study is the first systematic review of PN in APS. Although the pathogenesis of PN is poorly understood, small fiber dysfunction can result from microthrombosis, direct antibody binding to neuronal epitopes that lead to nerve dysfunction, or both. The latter hypothesis is supported by reported symptom improvement with immune system modulatory therapy (16, 17). The involvement of the central nervous system in APS is well known. However, the peripheral neurological manifestations are less described in the literature, with mononeuritis multiplex being the most common manifestation in 60% of our studies. The main nerves involved were sural, fibular, and median, with reports of associated carpal tunnel syndrome (7-15).

In 90% of the studies, the clinical diagnosis was complemented by electroneuromyography or skin biopsy. About 30% (n=3) confirmed the presence of PN using the combined method of nerve biopsy and electroneuromyography. In comparison, the remaining 60% underwent only one investigation, with the electroneuromyographic study, although frequently used, failing to assess the cause. Skin biopsy, on the other hand, is easy to perform and is emerging as the gold standard for diagnosing sensory and autonomic neuropathies of small fibers with an estimated sensitivity and specificity of around 90% (10).

In the evaluated studies, 40% (n=4) used anticoagulants to treat thrombotic symptoms, thus improving the symptoms of PN (7-15). One of the studies showed improved symptoms when using warfarin orally during the 2-year follow-up, without recurrence of the disease (15). In contrast, two patients needed methylprednisolone, followed by intravenous immunoglobulin.

Finally, some limitations were observed in the published studies, including the fact that the number of participants is still low. Future studies should involve large patient samples with longer follow-up, enabling a better understanding of this neurological manifestation in APS. The studies must address exclusively primary APS, since associated diseases such as SLP may induce PN. It is known that 7.6% of lupus patients have this neurological abnormality (18). Studies using standard methodologies to detect PN, such as electroneurography, are also desired, as well as the use of nerve biopsy and standardized methods for evaluating aPL. This study's strengths include considering studies with patients diagnosed according to international criteria for APS (19, 20).

Conclusions

The present study was a systematic review of all studies that evaluated PN in APS patients. Although uncommon, PN in APS should be considered, mainly in female patients with aPL positivity. Most cases were confirmed by electroneurography or nerve biopsy and had a good outcome.

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