Journal of Clinical & Experimental Cardiology
ISSN: 2155-9880

Ames et al., J Clin Exp Cardiolog 2014, 5:3
DOI: 10.4172/2155-9880.1000293

Review Article Open Access

Atherosclerosis in Primary Antiphospholipid Syndrome: Summary of Clinical and Pathogenic Evidence

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Abstract

The Antiphospholipid Syndrome (APS) was described in the early '80s as a combination of thrombosis, thrombocytopenia and recurrent miscarriages associated with persistent high titers of Antiphospholipid Antibodies (aPL). In subsequent years, it became apparent that aPL were also associated with premature atherosclerosis in Systemic Lupus Erythematosus (SLE) and more recently in primary APS (PAPS). The studies exploring atherosclerosis in PAPS were heterogeneous in conception and size, but overall, provided enough evidence that Intima Media Thickness (IMT) of carotid arteries and endothelial function are abnormal in PAPS. In keeping with the general view that atherosclerosis is a low grade inflammatory and "auto"immune disorder characterised by oxidative and nitrative stress, several studies have confirmed similar findings in PAPS, though a specific relation with the severity of atherosclerosis is lacking. Given its development at an earlier age than average, atherosclerosis should be taken into account in the overall management of PAPS patients as it may significantly add to the vascular risk.

Keywords: Atherosclerosis; Intima media thickness; Antiphospholipid syndrome

Introduction

The occurrence of arterial or venous thrombosis and recurrent miscarriages in the presence and persistence of Antiphospholipid Antibodies (aPL) detected by immunoassays or clotting tests defines the Antiphospholipid Syndrome (APS) [1]. Early observations suggesting that aPL contributed to atherosclerosis in Systemic Lupus Erythematosus (SLE) lead to testing the atherosclerosis hypothesis in primary APS (PAPS) through the measurement of Intima Media Thickness (IMT) in large enough PAPS series [2-11]. This review will survey the pathways associated with premature atherosclerosis in PAPS as they temporally appeared in the scientific literature, and will discuss how these reports support the concept of atherosclerosis as a low grade inflammatory and immune process.

Evidence for Atherosclerosis in PAPS

Atherosclerosis detected as intima media thickening

The measurement of IMT via high-resolution ultrasonography of carotid arteries is a surrogate but established method to identify patients at early risk of atherosclerosis that has been employed to detect sub-clinical atherosclerosis in several PAPS series [3]. Two of these series did not find intima-media thickening in PAPS: in one study, IMT and plaque prevalence were similar in 45 PAPS patients with deep vein thrombosis and in non-APS thrombotic controls matched by age, sex and other vascular risk factors. Having examined the abdominal aorta, the carotid and femoral arteries the authors concluded that atherosclerosis was not a feature of their PAPS cohort [4]. Another survey of PAPS, SLE related APS and normal controls revealed similar IMT across groups though there was a higher plaque frequency in SLE related APS (37.5%) vs. PAPS (8%) [5]. Similarly plaques were detected in 14% of SLE related APS and in 9% of PAPS with no differences in IMT though plaques were more frequent in patients with prior arterial and venous thromboses [6].

On the other hand, 3 reports of PAPS patients showed greater IMT with a greater prevalence of plaques (21%) compared to an equal number of age and sex matched non-thrombotic controls (3%) [7-10]. These studies have some limitations in that PAPS patients, by definition, are characterised by persistence of aPL and thrombosis, and any such study should include both healthy (normal) and thrombotic controls with persistence of the thrombotic risk factor. With this in mind, we provided conclusive evidence for premature atherosclerosis defined as increased IMT in PAPS patients over 40 years of age compared to younger PAPS patients, and to thrombotic and non-thrombotic controls matched by age and sex. Interestingly, diastolic blood pressure was an independent predictor of the IMT of the carotid artery [11]. Table 1 summarises the IMT measurements and plaque prevalence of the above mentioned studies while Table 2 shows the distribution if IMT by age tertiles from our study [11].

Atherosclerosis detected as arterial stenosis and heart valve disease

Stenosis of several arteries may be viewed as an athero-thrombotic complication in PAPS [12]. Renal artery stenosis of may have further implication with regards to increased arterial blood pressure that may adversely affect atherosclerotic cardiovascular disease [13]. In addition, thickening of heart valves in PAPS may bear atherosclerotic significance. A trans-oesophageal ultrasound study on 31 patients revealed functional and structural defects in the mitral valve of 84% of PAPS patients examined; valve lesions were more common in subjects with high titres of IgG anticardiolipin (aCL) and a history of arterial

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Received January 21, 2014; **Accepted** March 20, 2014; **Published** March 31, 2014

Citation: Ames PRJ, Lopez LR, Matsuura E, Margarita A (2014) Atherosclerosis in Primary Antiphospholipid Syndrome: Summary of Clinical and Pathogenic Evidence. J Clin Exp Cardiolog 5: 293. doi:10.4172/2155-9880.1000293

Table 1: Intima media thickness of carotid arteries in patients with primary antiphospholipid syndrome.

Reference No	4	5	6	7	8	9	10	11
Patients No	45	25	58	28	28	77	58	49
Mean age	47	38.6		40	NR	46	29	37
M/F	15/30			16-Dec	16-Dec	0/77	1/4	18/31
IMT CC (mm)		0.7		2.6	0.68	0.75	0.71	0.48
Plaque %	35.6	8	9		53		21	11
Thrombotic Controls No	40				26			49
Mean Age	47				NR			37
M/F	15/25							18/31
IMT CC (mm)					0.58			0.44
Plaque %	35							5.8
Healthy Controls No		40	89	28	38	77	58	49
Mean age		42		41	NR	47	29	37
M/F				16-Dec		0/77	4-Jan	18/31
IMT CC (mm)		0.61		1.2	0.58	0.64	0.59	0.41
Plaque %		15	?				3	5.8

Abbreviations: IMT: Intima Media Thickness; CC: Common Carotid Artery; NR: Not Reported. Study No 8 included as controls a mixture of patients with coronary artery disease and healthy subjects; Study No 10 included patients with systemic lupus erythematosus. Study No 7 used different parameters for IMT measurement.

Table 2: Intima-media thickness of carotid artery segments by age tertiles from Ames et al. [11].

	Intima-media thickness of common carotid (mm)			
	CTR	IT	PAPS	P
1st tertile	0.347 ± 0.030	0.386 ± 0.064	0.406 ± 0.090	0.05
2nd tertile	0.384 ± 0.047	0.405 ± 0.055	0.468 ± 0.088	0
3rd tertile	0.496 ± 0.074	0.528 ± 0.085	0.581 ± 0.119	0.03
	Intima-media thickness of carotid bifurcation (mm)			
1st tertile	0.412 ± 0.078	0.479 ± 0.083	0.438 ± 0.081	0.15
2nd tertile	0.446 ± 0.065	0.504 ± 0.085	0.529 ± 0.094	0.02
3rd tertile	0.557 ± 0.113	0.564 ± 0.093	0.693 ± 0.171	0
	Intima-media thickness of internal carotid (mm)			
1st tertile	0.320 ± 0.056	0.368 ± 0.091	0.366 ± 0.086	0.22
2nd tertile	0.374 ± 0.083	0.375 ± 0.061	0.460 ± 0.076	0
3rd tertile	0.444 ± 0.086	0.480 ± 0.077	0.546 ± 0.112	0.01

Abbreviations: CTR: Healthy Controls; IT: Inherited Thrombophilia; PAPS: Primary Antiphospholipid Syndrome
1st tertile: 16 patients (10M, 6F), mean age 26 ± 4.4 years
2nd tertile: 16 patients (10M, 6F), mean age 36 ± 2.7 years
3rd tertile: 17 patients (11M, 6F), mean age 49 ± 8.5 years

thrombosis, particularly cerebrovascular events [14]. Another series on 40 patients revealed mitral valve thickening in 82% of PAPS patients in strong association with IgG aCL titre with significant progression of valve lesions at a five year of follow-up [15,16]. These findings may have strong repercussions at the time of heart valve surgery where 50% of patients may develop complications with a mortality rate of 12.5% [17].

Atherosclerosis and endothelial dysfunction

Endothelial dysfunction may develop very early in the course of atherosclerosis and may match early IMT changes in pathophysiologic significance. An abnormal ankle-brachial-index was more common in PAPS (19%) than in healthy controls group (4%) though these findings were not corrected for confounders such as hypertension, obesity and hypercholesterolaemia [18]. Flow mediated vasodilatation was consistently lower in PAPS than in controls particularly in patients with arterial disease [8,9,19-22].

Atherosclerosis findings on histology

The pattern of vascular involvement in PAPS is one of histologic intimal/medial hyperplasia and radiologic fibromuscular hyperplasia, but it is unclear whether this represents a distinct vasculopathy [23-25].

Atherogenic Pathways in Paps

Traditional and non-traditional risk factors for atherosclerosis

Hypertension, hypercholesterolemia, diabetes mellitus, obesity, smoking, sedentary life style and family history are traditional risk factors for atherosclerosis identified by the Framingham Heart Study [26]. While some of these factors may be operative in APS related to SLE, their role in primary APS seem to be less dominant [2]. Less than 5% of our PAPS patients have any of these risk factors, others may have up to 36% traditional risk factors while the use of matching controls with similar risk factors still identified aPL as an independent contributor to atherosclerosis. In another survey at least 50% of PAPS patients had one traditional risk factor [1,15,16].

Haemostatic variables and atherosclerosis

Plasma Fibrinogen (FNG) and von Willebrand Factor (vWF) have been identified as risk factors for thrombosis and atherosclerosis [27,28]. An early study revealed that these variables were differentially associated with arterial and venous occlusions in PAPS regardless of sex [29]. More recently, plasma FNG was identified as an independent predictor of IMT of carotid arteries in PAPS [10,30]. Moreover PAPS patients presented coagulation activation, depressed fibrinolysis

and elevated D-dimers, a marker of heightened fibrin turnover [31]. Elevated Plasminogen Activator Inhibitor (PAI), a marker of depressed fibrinolysis and a risk factor for atherosclerosis, correlated with IMT of carotid arteries and to heightened Factor XIII activity that tightens the fibrin clot making it more resistant to plasmin lysis [30,32,33]. Therefore PAPS patients are in a state of accelerated fibrin turnover and fibrin deposition on the vessel wall that is a recognized early phenomenon in atherogenesis [34].

Oxidative stress, oxidative low density lipoprotein ligands and atherosclerosis

Paraoxonase (PON) is an enzyme present in the arterial wall and associated to HDL in plasma [35,36]. Reduced PON activity (PONa) contributes to lipid peroxidation, a major process in atherosclerosis [37]. Specific by-products of lipid peroxidation induce transcriptional activation of the genes that promote vascular adhesion molecules and monocyte chemo-attractant proteins shifting the endothelium towards a pro-adhesive and pro-thrombotic phenotype [38]. PAPS is characterised by reduced PONa, greater IMT and enhanced lipid peroxidation [9,39]. The former and the latter were respectively inversely and positively correlated to aPL titres, all contributing to the athero-thrombotic tendency of PAPS via the over-generation of isoprostanes linked to platelet activation and to heightened diastolic blood pressure [40].

Low-Density Lipoproteins (LDL) contain phospholipids, free cholesterol, cholesteryl esters, triglycerides and apolipoprotein B (apoB) that are all susceptible to oxidation [41]. A weak in vitro oxidation induced by copper generates Cu2+-oxLDL that interacts with lysine residues on β2GPI. This interaction is initially electrostatic and reversible but later progresses to a stable bond involving a Schiff base formation [42]. In this process, β2GPI neutralizes the negative charges generated by Cu2+-oxLDL undertaking a possible anti-oxidant and anti-inflammatory effect alongside its anticoagulant and anti-apoptotic properties [43]. Since oxLDL stimulates the release of several soluble inflammatory and adhesion molecules, induces a pro-thrombotic endothelial surface and promotes inflammation by attracting monocytes and T-lymphocytes to the arterial intima. The possibility that β2GPI might blunt all these activities is highly attractive. On the other hand, given the strong immunogenic properties of oxLDL and β2GPI, it is possible that autoantibodies against β2GPI-oxLDL may hamper these positive effects of β2GPI [44]. From the clinical standpoint, IgG anti-β2GPI-oxLig1 independently predicted intima media thickness of different carotid segments and was inversely related to PONa highlighting an important role of oxidative/antioxidant systems in PAPS related atherogenesis [45].

Monocytes/macrophages and atherosclerosis

Monocytes/macrophages have receptors for LDL that should prevent lipid over-loading. Native LDL is taken up by specific LDL receptor whereas oxLDL is taken up by scavenger receptors [46]. The presence of β2GPI and IgG β2GPI auto-antibodies increases the macrophage uptake of I131-Cu2+-oxLDL in keeping with a pro-atherogenic role of IgG anti-β2GPI antibodies [47]. The uptake of the immune complexes is likely mediated by macrophage Fcγ receptors rather than scavenger receptors. During the uptake process, circulating monocytes may have adhered to endothelial cells and started their migration into the intima of the arterial wall where they contribute to the intima media thickening typical of atherosclerosis alongside other cellular components.

Soluble CD14, neopterin and atherosclerosis

The expression of CD14 on the membranes of monocytes increases with the differentiation of monocytes into macrophages. Shedding of CD14 induced by serine proteases leads to a soluble CD14 (sCD14) present in plasma [48]. Neopterin (NPT) is produced in large amounts by human monocytes/macrophages upon stimulation with the cytokine interferon-γ released by activated T-lymphocytes [49]. Whereas mCD14 complex is expressed on macrophages and endothelial cells within the atherosclerotic plaque, plasma sCD14 shows no relation with stable coronary artery disease or carotid IMT [50-54]. NPT is associated with different stages of peripheral vascular disease and with carotid atherosclerosis, and predicts coronary artery disease progression [55-57]. In support of a role for monocytes/macrophages in the vascular pathogenesis of PAPS, serum levels of sCD14 and neopterin were elevated in thrombotic PAPS compared to thrombotic and normal controls. Moreover in PAPS patients the number of thrombotic events predicted NPT whereas arterial disease predicted NPT and sCD14 [58].

Antibodies against high density lipoprotein and atherosclerosis

High-Density Lipoprotein (HDL) protects against atherosclerosis by inhibiting LDL oxidation by way of its PONa content [36]. Apolipoprotein A-I (ApoA-I), the major protein component of HDL stabilizes the molecule and protects humans from cholesterol accumulation in tissues [59]. In this regard, ApoA-I possesses nearly identical information as HDL in terms of risk prediction for future cardiovascular disease [59]. Any interference with HDL components could thus compromise the protective role of HDL. In the context of autoimmune diseases, HDL represents a likely target for auto-reactivity. Elevated levels of anti-HDL have been reported in PAPS in association with decreased PONa and HDL [60,61]. Moreover low levels of Apo A and HDL inversely related to C-Reactive Protein (CRP) in keeping with an anti-inflammatory activity of these lipoproteins in PAPS [61].

Inflammation, nitrative stress and atherosclerosis

CRP, the first acute-phase protein identified, is a strong predictor of first clinical events, recurrent events, coronary heart disease end-points and ischaemic stroke [62]. Serum amyloid A (SAA) is an apolipoprotein that circulates in plasma in association with HDL [63-65]. Several observational and prospective studies show that SAA parallels CRP with regards to cardiovascular disease prediction, although the absolute level of risk is generally much smaller [66-69]. Plasma concentrations of CRP and (SAA) are elevated in patients with thrombotic PAPS compared to thrombotic and normal controls and suggest that PAPS is a low grade inflammatory disease. Moreover, the number of thrombotic events was an independent predictor of SAA [58]. Conversely, CRP was also an independent predictor of crude plasma Nitro-Tyrosine (NT), a marker of nitrative stress, implying that low grade inflammation and nitration may be related phenomena in thrombotic PAPS [70]. Nitration of plasma proteins is partially accomplished by peroxynitrite anion ($ONOO^-$) that results from the interaction of superoxide anion (O_2^-) released by monocytes, neutrophils and endothelial cells with nitric oxide (NO_2) produced by endothelial cells [71]. The oxidative inactivation of NO by superoxide anion (O_2^-) is the prevalent mechanisms leading to decreased bioavailability of NO, an early phenomenon in atherosclerosis, associated with impaired vasomotor tone and increased platelet reactivity [72]. PAPS patients, particularly patients with arterial disease, show decreased mean plasma nitrite (NO_2^-) concentration [70].

Conclusion

Management of PAPS related atherosclerosis

At present we do not know how to manage PAPS related atherosclerosis. Control of modifiable risk factors such as the lipid profile is intuitive. However the progression of heart valve lesions in PAPS is worrying and warrants clinical intervention [16]. Treatment may be directed at managing the effects of aPL antibodies or at decreasing aPL titres. Given their positive effects on the immune system, on the vascular endothelium and on PONa (reviewed in [73]), statins may be suitable candidates within the context of a clinical trial. Indeed, an in vitro study showed that pravastatin was effecting at reverting the pro-adhesive and pro-thrombotic phenotype induced by aPL on endothelial cells, and a one month interventional trial with fluvastatin restored monocyte function in patients with APS [74,75]. Probucol ameliorated coagulation activation and lipid peroxidation in PAPS [76]. Aspirin may be useful for the primary prevention of arterial events in aPL positive subjects that may go on to develop atherosclerosis [77]. Anti-CD20 accomplished lowering of aPL titers in some PAPS patients but not others [78].

Concluding remarks

Atherosclerosis is a clinical manifestation that further qualifies PAPS as a systemic vascular disease. PAPS is a relatively rare disorder and any interventional trial would require homogenous populations in a multicentre fashion to evaluate suitability of anti -atherosclerotic drugs and dosages.

Acknowledgements

The work in this review was supported by www.SenitFoundation.co.uk, Scotland, UK and by www.FondazioneAPS.com, Italy.

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This article was originally published in a special issue, **Atherosclerosis Vascular disease-2nd Edition** handled by Editor(s). Dr. Zhonghua, Sun Department of Imaging and Applied Physics Curtin University, Australia