Primary antiphospholipid syndrome and antiphospholipid syndrome associated to systemic lupus: Are they different entities?

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Abstract

Primary antiphospholipid syndrome (PAPS) and antiphospholipid syndrome associated to lupus (SAPS) have several overlapping characteristics. As systemic manifestations are also reported in patients with PAPS, and as a subgroup of PAPS patients could evaluate to a SAPS, the differentiation between the two types of APS could be performed based on the clinical experience of the medical teams and is related to a variety of clinical, biological, histological and genetic features.

Several data are available in the literature with respect to the identification of distinctive features between these two entities. However, there are some limitation in the interpretation of results issued from studies performed prior to updated Sydney criteria.
Based on recent data, a certain number of features more frequent in one type of APS as compared to the other could be distinguished.
The major differentiation between these two entities is genetical. New genetic data allowing the identification of specific subgroups of APS are ongoing.

Keywords
Antiphospholipid syndrome, primary antiphospholipid syndrome, secondary antiphospholipid syndrome.

Take-home messages

- In primary and secondary antiphospholipid syndrome the major clinical manifestations and the biological features are similar, but they are two distinct entities with a trend for the prevalence of specific features in one and the other type.
- Differences between primary and secondary APS concern clinical and laboratory features, genetic and histological aspects.
- The main differences between PAPS and SAPS are related to their genetical features.
- Future studies on the genetic factors in APS are expected to identify specific genetic features in PAPS which evolve into SLE.

1. Introduction

Antiphospholipid syndrome (APS) combines thrombotic (venous and/or arterial) and/or obstetrical manifestations, along with biological anomalies related to the presence of antiphospholipid antibodies (aPL) (circulating lupus anticoagulant, anticardiolipin antibody (aCL) or anti-β2glycoprotein I antibody(aβ2GPI)).

APS clinical-biological classification criteria were specified in 1999 and revised in 2006 *(1).* Diagnosis is based upon clinical and laboratory criteria. In order to define APS, at least one clinical criterion combined with at least one biological criterion are required.

Diagnostic classification criteria for APS are vascular thrombosis, pregnancy morbidity (one or more unexplained deaths of morphologically normal foetus beyond the 10th week or one or more premature births before the 34th week of gestation or three or more unexplained consecutive spontaneous abortions before the 10th week of gestation) and the presence of aPL (aCL antibodies, aβ2GPI antibodies, lupus anticoagulant) *(1).*

Exact aetiology is unknown but is thought to be multifactorial. There is, in some families, strong evidence of a genetic component. aPL are thought to interfere with the function of binding proteins and activate endothelial cells inducing a proinflammatory and procoagulant state in blood vessels which leads to thrombosis.

The occurrence of thrombosis in patients with APS has been explained by several physiopathological hypotheses, including:

- activation of various cells, including endothelial cells, monocytes and platelets *(2)*
- acquired activated protein C resistance (*3)*
- tissue factor expression, reduced tissue factor pathway inhibitor (TFPI) (*4*).
- complement activation (*5)*
- resistance to the action of annexin A5 (*6-8).*

Additionally to well-known mechanisms including activation of endothelial cells, monocytes, and platelets, and/or inhibition of natural anticoagulant and fibrinolytic systems by aPL new mechanisms were recently described *(9).*

Therefore, the antibodies against the domain I of β2 glycoprotein I (β2GPI) are increasingly recognized as the main pathogenic subset in APS; annexinA2 and toll-like receptor (TLR)4 have been identified as the main receptors for β2GPI/anti-β2GPI antibodies on target cells, and additional co-receptors such as TLR1, TLR2 and TLR6 were reported. Upon binding, aPL trigger intracellular mediators such as nuclear factor kappa B and mammalian target of rapamycin *(10-12).*

2. Pathophysiological, histopathological and clinical characteristics

2.1. **Symptoms**

The disease appears in young adults, but it can occur at all ages. Classical signs are represented by thrombosis (most commonly in the deep limb veins) and obstetrical complications (recurrent foetal loss and preeclampsia) *(10-14).* Clinically, the series of events that lead to hypercoagulability and recurrent thrombosis can affect virtually any organ system, including the following:

- Central nervous system (stroke, sinus thrombosis, seizures, chorea, reversible cerebral vasoconstriction syndrome)
- Cardiac (myocardial infarction, Libman-Sacks valvulopathy, diastolic dysfunction)
- Renal (thrombotic microangiopathy) antibodies
- Hematologic (thrombocytopenia, haemolytic anaemia)
- Pulmonary (pulmonary embolism, pulmonary hypertension)
- Dermatologic (livedo reticularis, purpura, infarcts/ulceration)
- Ocular (amaurosis, retinal thrombosis)
- Adrenal (infarction/haemorrhage)
- Musculoskeletal (avascular necrosis of bone)
- Peripheral nervous system (peripheral neuropathy including Guillain–Barré syndrome) *(10-14).*

A medical history of headaches or migraines could be one of the earliest manifestations of APS *(15).*

Recurrent thromboses are common. A very rare accelerated form of APS is catastrophic APS that occurs most frequently in women in their 30s and can lead to massive venous thromboembolism along with respiratory failure.

2.2. **Primary and secondary APS**

The experts accorded to make the distinction between primary APS (PAPS) and APS secondary to other conditions *(1, 16).* APS may occur as isolated, without any associated condition (primary APS or in the context of a background disease, particularly autoimmune, mainly systemic lupus erythematosus (SLE) (secondary APS).

Although the major clinical manifestations and the biological features are the same in both types, they are two distinct entities with a trend for the prevalence of specific features in one and the other type of APS.

As revealed by some authors, even though there are classification criteria for SLE and APS, the distinction between primary and secondary APS can be difficult, since primary APS may

present with proteinuria, pleurisy, seizures, psychosis, hemolytic anemia and thrombocytopenia. In 1993, Piette et al. proposed exclusion criteria for primary APS such as malar or discoid rashes, oral or pharyngeal ulceration, arthritis, pleuritis, pericarditis, proteinuria greater than 0.5 g per day, lymphopenia of less than 1000 µl, anti-DNA or anti-ENA antibodies, ANA of greater than 1:320, and the use of drugs known to induce aPL. However, these exclusion criteria have not been used by clinicians (*17*).

The differences between primary and secondary APS were considered by several reports and they concern clinical and laboratory features, genetic and histological aspects *(18-28).*

2.2.1. **Are they distinct?**

Primary antiphospholipid syndrome and antiphospholipid syndrome associated to lupus have several overlapping characteristics (*21).*

Multiorgan manifestations similar to classical typical clinical features of systemic lupus erythematosus lupus are also reported in patients with PAPS *(22*).

Different SLE biological features such as an autoantibody against chromatin and complement activation have been also described in patients with PAPS (*22-29*).

In a cohort of 108 patients Weber et al. have suggested the occurrence of an intermediate group of patients with antiphospholipid syndrome and lupus-like disease, but with features more common to PAPS *(30).*

Tarr et al. have suggested that PAPS could be the forerunner of SLE (*23*). In 7.2% of the cases in their series PAPS appeared 5.5 years before the onset of lupus (*23)*.

In their experience, this subgroup of patients presented with more thrombotic and less inflammatory complications than SLE patients without a prior or with a following secondary APS (*23)*.

Distinct polymorphisms of genetic factors have been associated with SLE and PAPS, suggesting that these entities are variants within a continuum of the same disease (*22*).

Recently, Taraborelli et al. reported in a retrospective multicentre study in one hundred fifteen patients, followed between 1983 and 2014, with a median follow-up of 18 years (range 15-30), that 14% of primary APS patients developed an autoimmune disease and 13 (11%) a connective tissue disease (*24).*

Some authors suggested that some biological markers could be an useful tool for identifying PAPS subgroup which will later became a SAPS (*31*).
Therefore, Andreoli et al. have suggested that antinucleosome antibodies could be predictive for outcome of PAPS evolving into SLE (*31*).
Medium-high titre anti-nucleosome antibodies were found in 46% of PAPS patients, and more frequently in subgroup of patients with features of "lupus like disease"(*31).*

2.2.2. **Clinical and laboratory features in primary and secondary APS**

As regard clinical and laboratory features in primary and secondary APS, several data are available in the literature**.**
Nevertheless, some difficulties in the interpretation of data from studies performed prior to updated Sydney criteria unable strong formal conclusions as regard certain distinctive features between these two entities.

In the study of Vianna et al., patients with PAPS and patients with APS plus SLE had differences which concerned autoimmune haemolytic anaemia, endocardial valve disease, neutropenia, and low C4 levels, all of which occurred more frequently in patients with APS plus SLE (p values: <0.05, <0.005, <0.0l, and <0.00l, respectively) (*25)*. In their series, no patient with PAPS had either anti-DNA or anti- extractable nuclear antigen antibodies, and, moreover, these patients had a significantly lower prevalence of antinuclear antibodies (41%) than patients with APS plus SLE (89%) *(25)*.

For Weber H et al. the main differences between PAPS and SAPS consisted in statistically significant differences for positive Coomb's test, leukopenia, lymphocytopenia, antinuclear antibodies, anti-DNA and anti ENA antibodies and hypocomplementemia *(30).*

It has been further suggested that the male/female ratio in PAPS is higher than in SLE and in secondary APS *(25).* Thrombocytopenia, haemolytic anaemia and livedo reticularis were more frequently found in patients with APS secondary to SLE, whereas arterial occlusions and recurrent foetal loss have higher frequency in PAPS *(25)*.
Freitas MV et al reported a trend in the association of arterial thrombosis to PAPS, and of lymphopenia, antinuclear antibodies and VDRL to secondary APS *(32).*

Moss KE and al compared renal disease severity and outcome in three groups of patients: 20 patients with primary antiphospholipid syndrome, 25 patients with antiphospholipid

syndrome secondary to systemic lupus erythematosus (SLE) and 275 patients with systemic lupus erythematosus SLE alone (*33).*

In this cohort, patients with PAPS were less likely to develop end-stage renal failure, as no patients with PAPS developed end-stage renal failure compared with 5.9% of patients with SAPS and 16.9% of patients with systemic lupus erythematosus alone (*33).*

In a large retrospective cohort of 637 patients Soltesz P et al. comparatively evaluated the clinical and laboratory features of primary and secondary to SLE APS patients *(34*).
Stroke was more frequently found in SAPS (p=0.04); and predominantly associated to LA and IgG aCL *(34).*

Venous thrombosis was more frequently associated to LA (p<0.0001), and coronary, peripheral artery and carotid thrombosis in patients with aCL IgG and IgM (p<0.0001) (*35*).
As regard fetal loss, no differences between groups were reported by some authors, (*34*), but these data are controversial *(35-37).*

Boura et al. found more miscarriages in primary APS *(p<0.05) (35),* data in contrast, with those from a cross-sectional study of consecutive patients in the Hopkins Lupus Center *(36).*
Therefore, the frequency of thrombosis and pregnancy loss was higher in SAPS than in primary APS in the Hopkins Lupus cohort *(36).*

Recurrent miscarriages, and livedo reticularis occurred more often in SAPS by other groups (*38).*

In the study of Marai et al. clinical features of patients with primary or secondary syndrome were similar *(37)*. Patients with SAPS had a higher prevalence of hemolytic anemia (28.6% v 3.3%; P = 0.001), and antinuclear antibodies (75% v 12.9%; P = 0.0001) *(37).*
Moreover, the authors observed that the clinical manifestations were similar in Israeli and non-Israeli patients *(37)*.

A large diversity of clinical symptoms and immunological disturbances were more frequent in SAPS patients.
Some authors reported a higher prevalence of pulmonary embolism and deep venous thrombosis in primary APS (*38).*

Chwalińska-Sadowska H et al. further reported that PAPS patients were younger at the onset of the disease compare to SAPS patients and that men/female ratio was lower in patients affected with SAPS (*38).*

A Russian prospective trial in 93 patients including 34 patients with PAPS and 59 with APS secondary to SLE (SAPS)reported that vascular manifestations were predominant in primary APS and systemic manifestations were predominant in those with SAPS (*39).*

Pons Estel et al. have recently focused on the primary and secondary APS similarities and differences *(40)*. Therefore, the presence or lack of SLE might modify the clinical or serological expression of APS. Secondary APS patients with associated SLE more frequently present arthralgias, arthritis, autoimmune hemolytic anemia, livedo reticularis, epilepsy, glomerular thrombosis, and myocardial infarction *(40).*

The aPL (aCL, aβ2GPI, LAC) antibody profile in PAPS versus SAPS has been also focused, although, little literature is available on this topic.

Different reports found that there were no differences in aPL profile between primary and secondary to SLE APS patients *(34-35, 37, 39); and* no correlation between the antibody titers (LA, IgG aCL, IgM aCL) and clinical manifestations *(37).*

Some authors reported that anti annexinV antibodies occurred more often in SAPS, and IgM aCL, LAC, anti beta2GP1, oxyLDL antibodies in primary APS (*38).*

In the cohort of Alarcon Segovia et al. patients with PAPS tend to have more persistently positive and higher levels of aCL than those with secondary APS *(41).*
In the series of Djokovic LA was more frequently reported in PAPS (*42),* data in contrast with results available from the larger Europhospholipid cohort *(26).*

Type of aPL	PAPS	SAPS	References
acL	+ more positive and higher levels		*41*
Lupus anticoagulant	+		*42*
Lupus anticoagulant		+	*26*
No differences	+	+	*34, 37, 39*

Table 1. Antiphospholipid antibodies profiles in primary and secondary APS.

Several data are available from the Serbian national cohort APS study *(42-45).*

In all studies of this team certain classes of aPL were associated with distinct clinical manifestations in primary and secondary APS *(42-45)*.

The distribution of aPL in the primary APS and SLE groups revealed a highly significant difference in the presence of aCL IgG and IgM, and β2GPI IgG antibodies (*42)*. Lupus anticoagulant was present alone in 47 patients (18.1%) with primary APS and only 7 (6.1%) with SLE. aCL antibodies were present alone in 43 (16.5%) with primary APS and 22 (19.3%) with SLE. Anti-β2GPI antibodies were present alone in 13 (5.0%) with primary APS and 5 (4.4%) with SLE (*43)*.

As regard cardiac and neurological manifestations in APS, the presence of aCL IgG was more common (p=0.001) in SAPS and LA in PAPS patients (p=0.002). In PAPS high ß2GPI IgM levels (>100PLU/ml) were more common in epilepsy (p=0.00001) *(43).*
In SAPS high ß2GPI IgM levels were more common in transient ischemic attack (p=0.029) and high ß2GPI IgG levels (>100PLU/ml) were more common in epilepsy (p=0.035) *(43).*
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Chorea, migraine and epilepsy occurred more often in SAPS. In SAPS statistical significant correlations were found as regard the presence of aCL IgG and acute ischemic encephalopathy, aCL IgM and epilepsy, ß2GPI IgG and chorea *(43).*
.
Headache and depression were more common in PAPS *(43).*
.
In PAPS there was statistical significance considering the presence of aCL IgM and migraine, and ß2GPI IgM and TIA and epilepsy. LA was linked to depression, transient global amnesia and migraine in PAPS *(43).*

Patients with non-stable angina pectoris were more likely to develop TIA in both PAPS and SAPS, epilepsy and transient global amnesia in PAPS and acute ischemic encephalopathy in SAPS *(43).*

A prospective clinical study examined the association between subclasses of antiphospholipid and pulmonary manifestations in APS *(45).*

In SAPS, high aCL IgG levels (> 100 PLU/mL) were more common in major pulmonary arterial thrombosis (p = 0.006) and medium aCL IgG levels (41-99 PLU/mL) in adult respiratory distress syndrome (ARDS; p = 0.047) and fibrosing alveolitis (p = 0.002). aCL IgG antibodies were more common in SAPS (p = 0.037). In PAPS, fibrosing alveolitis was more

common in patients with medium β_2GPI IgM levels (p = 0.0001). LA correlated with pulmonary embolism (p = 0.03) and microthrombosis (p = 0.03) in SAPS, and with pulmonary microthrombosis (p = 0.03) in PAPS (*45)*.

Males were more likely to develop secondary pulmonary hypertension when diagnosed with PAPS (p = 0.019) *(45).*

As regards non criteria manifestations of APS and aPL antibody type and level, the same authors found that in PAPS, epilepsy correlated with ß2GPI-IgM, migraine with aCL-IgM, and thrombocytopenia with aCL-IgM, aCL-IgG, anti ß2GPI-IgG and LA (*43).*

Skin ulcerations occurred more frequently in IIc category patients and in patients with high levels of aCL-IgG and anti ß2GPI-IgG. Livedo reticularis was more prominent in PAPS with high levels of aCL-IgG. Significantly higher prevalence of thrombocytopenia was observed in patients with high levels of aCL-IgG and anti ß2GPI-IgG (*44).*

In SAPS epilepsy was related to high levels of anti ß2GPI-IgM and thrombocytopenia was correlated with aCL-IgG. Skin ulcerations were more prevalent in aCL-IgM positive SAPS patients and epilepsy more frequently in SAPS patients with high levels of anti ß2GPI-IgG (*44).*

These data are summarized in tables 2 and 3.

Type of aPL in PAPS	Features	References
LA	More common p 0.002 in PAPS	42
LA	depression	*43*
LA	transient global amnesia	*43*
LA	migraine	*43*
LA	pulmonary micro-thrombosis (p = 0.03)	*45*
LA	thrombocytopenia	44
anti ß2GPI IgM levels (High titers >100PLU/ml))	epilepsy (p=0.00001)	*43*
anti ß2GPI IgM	transient ischemic attack	*43*
anti ß2GPI IgM levels (medium anti β_2GPI IgM titers)	fibrosing alveolitis (p = 0.0001).	*45*

anti ß2GPI-IgG, aCL-IgM, aCL-IgG, and LA	thrombocytopenia	44
aCL-IgG and anti ß2GPI-IgG (high levels)	Skin ulcerations Livedo reticularis was more prominent in PAPS with high levels of aCL-IgG.	*44*
aCL-IgM	migraine	*43*

Table 2. Correlations between aPL antibodies type and clinical manifestations in PAPS

Type of aPL in SAPS	Features	References
aCL IgG antibodies	were more common in SAPS (p = 0.037).	*45*
high aCL IgG levels (> 100 PLU/mL)	major pulmonary arterial thrombosis (p = 0.006)	45
aCL IgG,	acute ischaemic encephalopathy	*43*
aCL-IgG	thrombocytopenia	44
aCL IgM	Epilepsy Skin ulcerations	44
LA	correlated with pulmonary embolism (p = 0.03)	*45*
LA	correlated with microthrombosis (p = 0.03	*45*
high ß2GPI IgM levels.	common in transient ischaemic attack (p=0.029)	*43*
high ß2GPI IgG levels (>100 UI GPL)	epilepsy (p=0.035).	*43*
ß2GPI IgG	chorea	*45*

Table 3. Correlations between aPL antibodies type and clinical manifestations in SAPS

As regard traditional risk cardiovascular factors, they were comparable between patients with primary and secondary APS, except for a high frequency of low HDL-c in primary APS patients (*46*).

The most important and relevant data arise from the large 1000 patients Europhospholipid trial (*26, 27)*.

In the 10 year-follow-up of the “Euro-phospholipid” trial, SLE-associated APS patients presented more frequently arthralgias (31.1% vs 8.1%) and arthritis (21.2% vs 2.8%), leucopenia (14.4% vs 2.4%), autoimmune hemolytic anemia (15.9% vs 2.1%), *livedo reticularis* (21.2% vs 6.9%), epilepsy (6.8% vs 1.2%), glomerular thrombosis (3.0% vs 0.2%) and myocardial infarction (3.8% vs 1.2%) compared with primary APS patients. Primary APS patients developed more frequently superficial thrombophlebitis (0% vs 1.9%) and fetal morbidity such as birth prematurity (40.0% vs 72.3%) and intrauterine growth restriction (1.0% vs 51.1%) *(26).* As regards the different autoantibodies patterns, LA, antinuclear antibodies (ANA), anti-dsDNA, anti-Ro/SSA, anti-La/SSB, anti-RNP and anti-Sm antibodies were more frequent in patients with APS associated with SLE compared with primary APS ($p < 0.001$) *(26)*.

No lethal outcome has been observed in patients with primary APS patients as compared to SLE and APS secondary to SLE patients, suggesting a better prognosis in PAPS (*33).* However, no differences in survival were found in the large Europhospholipid cohort after a period of 10 years of follow-up *(26).*

In the “Euro-Phospholipid” project, the mortality rate was similar in both groups, as 6.8% of patients with APS associated with SLE and 7.1% of patients with primary APS had a lethal outcome *(26)*.

However, the differences in clinical and serological manifestations reported in these series could also be related to different geographical origins *(47).*
Mejía-Romero R et al reported that latin American mestizo patients with primary APS have a wide variety of clinical and immunological manifestations with several differences in their prevalence in comparison with European white patients *(47).*

Several clinical manifestations were more prevalent in the Latin American mestizo 100 patients of their multinational cohort than in the European patients (transient global amnesia, pulmonary microthrombosis, arthralgias, and early pregnancy losses). Adversely, deep venous thrombosis, stroke, pulmonary embolism, and thrombocytopenia were more prevalent in European white patients *(47).*

2.2.3. **Genetic in primary and secondary APS**

Development of clinical features of APS in monozygotic twins suggest a genetic basis in the pathogenesis of anti-phospholipid syndrome *(48, 49*).

Freitas MVC et al reported a trend to association with DR53-asssociated alleles that was observed in PAPS patients as compared with secondary APS *(32)*. HLA-DRB1 and HLA-DQB1 profiles of primary and secondary APS are different, as for primary APS the HLA-DR7 is a genetic marker and for secondary APS the genetic markers are HLA-B8, HLA-DR2, HLA-DR3 *(20)*.
A genome wide analysis has identified several suggestive novel loci for APS; however, related to the low number of primary APS, no comparison could be performed between primary and secondary APS (*50).*

Muller-Calleja N et al have confirmed by genome wide analysis the significant associations of anti-B2GP1 IgG and APOH on chromosome 17, previously shown by candidate genes approaches, and of anti-domain 1 and MACROD2 on chromosome 20; and that antiphospholipid antibodies induce the expression of NAV3 in monocytes and endothelial cells (*51).*

It has been recently shown that MHC class II alleles have not only an impact on the quantitative production of aPL antibodies but also on their pathogenicity *(52).*

A recent study in a Japanese population with obstetric APS focussing on lupus anticoagulant demonstrated that a specific genotype of TSHR and C1D genes can be as risk factor for obstetric APS *(53).*

Recent data have shown decreased number of circulating $CD4^+CD25^+Foxp3^+$ Treg and $CD3^-CD19^+$ B cells in patients with systemic lupus erythematosus and secondary antiphospholipid syndrome, in SLE and primary APS (*54).*

Microarray expression profiling performed in monocytes further validated by RT-PCR of selected genes and western blot identified 555, 1224 and 518 genes differentially expressed in monocytes from SLE, APS plus SLE and APS patients compared with controls (*55).*
Among them 25-30% of differentially expressed genes were related to atherosclerosis and cardiovascular disease. Each disease had her own atherosclerosis and cardiovascular disease /Inflammation-related gene signature. The main differences between APS and SLE were the alterations in mitochondria biogenesis and function and oxidative stress found in APS; and the interferon signature and various genes mediating atherosclerotic/inflammatory signaling found in APS plus SLE and SLE patients. IgG-anticardiolipin (aCL) titers independently predicted both atherosclerotic and thrombosis in APS plus SLE (*55).*

2.2.4. **Histological features in primary and secondary APS**

The kidney appears to be a major target organ in both primary and secondary APS.

The renal manifestations of APS may result from thrombosis occurring at any location within the renal vasculature, that is, in the renal artery trunk or branches, intraparenchymal arteries and arterioles, glomerular capillaries, and the renal veins. The spectrum of these manifestations includes renal artery stenosis and/or malignant hypertension, renal infarction, renal vein thrombosis, thrombotic microangiopathy, increased allograft vascular thrombosis, and reduced survival of renal allografts. More recently no thrombotic conditions like glomerulonephritis have also been reported.

The role of biopsy is essential as inflammatory and thrombotic lesions require different therapeutic approaches *(56).*
Sciascia S et al have reported that the renal manifestations in APS are various and that renal prognosis is affected by the presence of aPLs in patients with lupus nephritis *(56)*.

It has been reported that primary APS-associated nephropathy has slower progression and rarely leads to end-stage renal failure *(57).*

The comparison between primary and secondary APS histological renal lesions revealed that glomerular thrombotic lesions were present in both types of APS, but immune complex disease were considered as specific to secondary APS (*58).*

All the data as regard current knowledge with respect to differences and potential differences between primary and secondary APS are summarized in the table 4.

	Primary APS	**Secondary APS**	**P value when available**	**Reference**
GENETIC				
		HLA-B8		*20*
	HLA DR7	HLA-DR2 HLA-DR3		
	DR53-asssociated alleles			*32*
	alterations in mitochondria biogenesis and	IFN Signature and various genes mediating atherosclerotic /inflammatory signaling		*55*

	function and oxidative stress. decreased numbers of circulating $CD4^+CD25^+Foxp3^+$ Treg and $CD3^-CD19^+$ B cells	decreased numbers of circulating $CD4^+CD25^+Foxp3^+$ Treg and $CD3^-CD19^+$ B cells		*54*
HISTOLOGICAL				
		Immune complex disease		*58*
Slow progression nephropathy	**+**			*57*
Renal disease severity		**+**		*33*
Glomerular thrombosis		**+**		*26, 31, 40*
CLINICAL and LABORATORY				
Ratio male/female >	**+**			*25, 38*
Younger age	**Trend**			*38*
Vascular manifestations	**+**	**+**		*36, 38, 39*
****Controversial**				
Arterial thrombosis	**Trend**			*25, 32*
Superficial thrombophlebitis	+			*26*
Myocardial infarction		**+**		*26, 40*
Endocardial valve disease		**+**	p<0.005	*25*
Foetal loss and fetal morbidity such as birth prematurity and intrauterine growth restriction	**+**	**+**		*25, 26, 35, 36*
****Controversial**				
Systemic manifestations		**+**		*26, 39*
Arthritis		**+**	p < 0.001	*26, 28, 31, 40*
Arthralgias		**+**		*26, 40*
Livedo reticularis		**+**	p < 0.001	*25, 26, 28*
Epilepsy		**+**		*26, 40, 43*
Chorea		+		*43*
Migraine		+		*43*
Headache and depression	**+**			*43*
Males prone to develop secondary pulmonary hypertension	(p = 0.019)			*45*
Lupus anticoagulant	**+**	**+**		*26, 34, 37, 39, 42*
****Controversial**				
aCL	+more persistently positive and higher levels	**+**		*34, 37, 39, 41*
****Controversial**				
VDRL		**+**		*32*
Prevalence of ANA		**+**	p= 0.0001	*25, 26, 37, 40*

Presence of anti DNA antibodies		+		*25, 26, 40*
Anti-Ro/SSA, anti-La/SSB, anti-RNP and anti-Sm antibodies		+		*26*
Low C4		+	<0.00l,	*25, 40*
Autoimmune hemolytic anemia		+	p<0.05, p = 0.001	*25, 26, 31, 37*
Leucopenia		+	p < 0.001,	*26, 28*
Neutropenia		+	p<0.0l	*25*
Lymphopenia		+		*32, 40*
Thrombocytopenia		+	p < 0.001	*25, 28*
Low HDLc	+			*46*
Worse prognosis	+	+		*26, 33*

****Controversial**

Table 4. Summary of genetical, histological, clinical and biological features in primary and secondary APS.

3. Conclusion

According to these findings, there are several features that could characterize primary APS as compared to secondary APS.

Nevertheless, these data should be interpreted with much caution, especially with respect to biological and clinical features, but also to histological differences, as most of these studies were performed before the update of classification criteria in APS (*1*).

It should not be forgotten that for some authors PAPS and SLE is one single entity with various manifestations (*22)*.

Based on recent data and according to Sidney diagnosis criteria of APS, the features that could allow the distinction between primary and secondary APS are mainly the presence of systemic manifestations in SAPS such as arthralgias and arthritis, vascular manifestations and particularly myocardial infarction, *livedo reticularis*, epilepsy, chorea, migraine, leucopenia, autoimmune hemolytic anemia.

Moreover, glomerular thrombosis and more severe renal disease are observed in secondary APS patients (*26, 31, 40),* as well as probably more frequent renal lesions with immune complex disease *(58).*

In primary APS a higher percentage of superficial venous thrombosis *(26),* as well as a slower progression nephropathy are observed (*57).*

Additional features such as headache and depression, and secondary pulmonary hypertension were reported in some series as more frequently prevalent in PAPS (*43, 45*).

A trend for younger age and predominant male/female ratio could be observed by some authors in primary APS (*25, 38).*
As regard the aPL profiles in primary and secondary APS, data as regards LA and aCL are controversial *(26, 42, 34, 37, 39).*

Nevertheless, autoantibodies patterns are different in primary and secondary APS: antinuclear antibodies (ANA), anti-dsDNA, anti-Ro/SSA, anti-La/SSB, anti-RNP and anti-Sm antibodies being more frequent in patients with APS associated with SLE compared with primary APS ($p < 0.001$) *(26)*.

However, the most important features allowing the classification in primary and secondary APS are genetical. There is an increased body of evidence of genetical differences between these two entities.
Therefore, the main differences between PAPS and SAPS are related to their genetical features: alterations in mitochondria biogenesis and function and oxidative stress in PAPS and IFN signature and various genes mediating atherosclerotic/inflammatory signaling in secondary APS (*55).*

Future studies on the genetic factors associated with SLE and PAPS may allow the characterisation of these entities and identify if there are specific genetic features in PAPS which evolve into SLE.

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