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Enhanced type I interferon gene signature in primary antiphospholipid syndrome: Association with earlier disease onset and preeclampsia

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ABSTRACT

Objective: Recently, two studies demonstrated that a relevant percentage of primary antiphospholipid syndrome (PAPS) patients had an upregulation of interferon (IFN) genes. However, 20%–28% of these patients had anti-dsDNA, a highly specific systemic lupus erythematosus (SLE) autoantibody. This study aimed to determine the prevalence of the type I IFN signature in the peripheral blood mononuclear cells of PAPS patients without specific SLE autoantibodies and search for its clinical associations.

Methods: Fifty-three PAPS patients (Sydney's criteria) were consecutively selected and age-matched with 50 healthy controls. A third group of nonimmune-mediated thrombophilia patients was also included. The expression of 41 IFN-induced genes was analyzed using real time quantitative PCR. A principal component analysis determined which genes composed the IFN signature, and the z-score was calculated. An ROC curve defined the signature cut-off.

Results: Six genes remained in the IFN signature DNAJA1, IFIT5, IFI27, MX1, IFI6, and TYK2. The ROC cutoff was 3.9-fold (AUC = 0.706, S = 0.49, E = 0.86, PPV = 0.79, NPV = 0.61). The type I IFN signature was present in 49% of the patients with PAPS compared with 14.0% of the healthy controls and 17% of the nonimmune-mediated thrombophilia patients ($p < .0001$). The IFN signature was associated with a younger age at the first antiphospholipid syndrome event ($p = .023$) and with preeclampsia ($p = .032$).

Conclusion: Our results indicate that PAPS patients without lupus-specific antibodies have an enhanced type I IFN gene signature that is not observed in nonimmune-mediated thrombophilia. Also, this overexpression of type I IFN-regulated genes associated with an earlier onset of antiphospholipid syndrome event and preeclampsia.

1. Introduction

Antiphospholipid syndrome (APS) is an autoimmune vasculopathy that is mediated by autoantibodies, with thrombosis as its main clinical manifestation [1,2]. The presence of antiphospholipid antibodies, while relevant for confirming the diagnosis, does not seem to be sufficient to fully explain the pathophysiology of the disease, and a second trigger is usually needed [3]. In addition to the hypothesis of viral infection and inflammatory insult as possible triggers [4], it seems that toll-like receptors (TLR) and type I Interferon (IFN) could be possible adjuncts in this process, contributing for the thrombosis onset [5–10].

Type I Interferon (IFN) is known to be a key element in the pathogenesis of systemic lupus erythematosus (SLE), and APS is quite often associated with SLE [2,11]. About half of lupus patients have a predominant expression of interferon-induced genes in their peripheral blood mononuclear cells (PBMCs) [11]. This type I IFN signature was fairly studied in longitudinal studies of SLE patients, and although the IFN blood levels seem to be associated with disease activity [12], the genetic signature of this cytokine in the blood is generally stable and not useful to predict SLE flares [13,14]. However, it is noteworthy that the type I IFN signature is a marker of more severe disease subsets (with kidney, hematologic, and neurological involvement) [11,15] and is also a marker of serological manifestations, such as higher anti-dsDNA levels and higher serum B cell activating family factor (BAFF) and lower complement serum levels [15].

Recently, two important studies demonstrated that a relevant

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percentage of primary antiphospholipid syndrome (PAPS) patients showed an upregulation of IFN genes in their PBMCs [16,17]. In addition to this finding, van den Hoogen and colleagues also revised the publicly available data from a previous discordant study [17] and showed that, actually, there was an overexpression of type I inducible genes but at levels that were below the threshold used in the first study [18].This IFN signature was demonstrated in independent cohorts of well characterized PAPS patients, without clinical SLE features [16,17]. A comparison of this gene expression with SLE patients showed a more robust IFN signature in SLE than in PAPS patients, and they speculated that this signature might be a marker of patients who may develop more lupus features over time. It is noteworthy that 28% of the patients in one of these cohorts had anti-dsDNA positive antibodies, a highly specific SLE autoantibody [16].

Although the serological and clinical features of PAPS and SLE were described in these previous studies [16,17], there was no association with the IFN signature. Insignificant trends towards higher IFN scores were observed in the patients with primary APS with higher titers of ANA and anti-dsDNA antibodies [17]. Interestingly, the patients with primary APS treated with hydroxychloroquine and statins had lower IFN scores than the patients not taking these drugs [17].

Therefore, the aim of this study was to determine the prevalence of the type I IFN signature in the PBMCs of patients with PAPS without specific SLE autoantibodies and to search for the clinical and laboratorial associations.

2. Patients and methods

2.1. Patient selection

A total of 53 PAPS patients followed in the Rheumatology Division of a tertiary hospital were consecutively selected. All the enrolled patients were between 18 and 60 years old, met the Sydney's criteria [1] and had at least one thrombotic event, such as a PAPS feature. To reduce the treatment bias on the gene expression analysis, only thrombotic PAPS patients on anticoagulation with vitamin K antagonists were included. The exclusion criteria were the concomitance of any other autoimmune disease or immunosuppressive treatment, chronic viral infections (human immunodeficiency virus, B and C hepatitis), thrombophilia and neoplasms. It is important to emphasize that patients presenting with SLE specific autoantibodies (anti-dsDNA or anti-Sm) were also excluded from this study. A second group of 50 age-matched healthy controls was also selected. Since the healthy controls were not on anticoagulants, a third group (positive control group) of non-immune-mediated thrombophilia patients (such as hyperhomocysteinemia, protein S and C deficiency) who were all anticoagulated with vitamin K antagonists was also included. The nonimmune-mediated thrombophilia patients were also tested for aPL and viral serologies.

2.2. Study design

This was a cross-sectional observational study, and all the data (such as the demographic, clinical and laboratorial findings) were obtained through an ongoing electronic database. Antinuclear antibodies (ANA), specific SLE antibodies [anti-double stranded DNA (anti-dsDNA) and anti-Smith (anti-Sm)] and aPL antibodies [anticardiolipin (aCL) IgG/IgM, anti-β_2_Glicoprotein I (aβ_2GPI) IgG/IgM, and lupus anticoagulant (LA)] were obtained from this electronic database, which accounted for all the performed laboratory tests during the patient's follow-up. Antibodies were considered positive if they were present any time along the follow-up history. Other laboratorial tests, such as blood count, complement, urinalysis, viral serologies, lipids and inflammatory activity, were all performed using the same samples collected for the genetic analysis.

After signing the informed consent, the patients were subjected to a complete clinical evaluation, and blood samples were collected. This study was approved by the local Institutional Review Board (C.E.P. # 12563).

2.3. Methods

2.3.1. PBMC isolation and RNA quality assessment

The serum samples were collected in clotting tubes (stored at −70 °C) and in sodium-heparin tubes for the PBMC isolation. The PBMCs were isolated using a fast centrifugation with the Ficoll-Hypaque method and were then stored at −70 °C.

The RNA was isolated from the purified monocytes using the miRNA isolation Kit: miRNeasy mini kit (Qiagen) and automated equipment (Qiagen). The RNA quality was evaluated using the Agilent 2100 Bioanalyzer apparatus (Agilent Technologies®) and the RNA 6000 Nano LabChip kit (Agilent Technologies®). The software calculates a ratio between the 18S and 28S ribosomal bands for eukaryotic samples and generates the RNA Integrity Number (RIN) (ranging from 0 to 10). Only samples with RIN > 7 proceeded to the gene expression analysis.

The RNA samples were treated with one unit of DNAse I enzyme (Ambion®). After treatment, 1 μg of the RNA was used to generate the complementary DNA (cDNA) in a 20 μL reaction using the SuperScript III RNase H-Reverse Transcriptase, 10 mM dNTP Mix, Oligo (dT) 12–18 Primer, Ribonuclease H and RNaseOUT Recombinant RNase Inhibitor (all from Invitrogen, Carlsbad, CA).

2.3.2. Real-time PCR (RT-PCR)

The expression of 41 IFN induced genes was analyzed using real time quantitative PCR (TaqMan Low Density Array – TLDA -from Life Technologies). These 41 genes (Table 1) were chosen because they are known to be regulated by type I IFN, and they were previously described in important pathways of SLE pathogenesis according to GWAS [19–21]. Genes that did not amplify properly were excluded from the analysis. For the relative expression calculation, all the results were normalized against the expression of 3 housekeeping genes (chosen by GeNorm algorithm). The fold change values were determined from the normalized CT values using the qbase+ software. Genes whose expressions were significantly different between the patients and controls proceeded to a principal component analysis (PCA). The PCA defined 6 genes for the IFN signature that represented 95% of the variance of all the relevant genes.

2.3.3. Calculation of the type I IFN scores

Of the 36 properly amplified genes, 11 genes clearly differentiated the patients from the healthy controls, including DNAJA1, EIF2AK2, IFI27, IFI35, IFI44, IFI6, IFIT5, IRF7, MX1, STAT1, and TYK2. The PCA selected 6 genes (DNAJA1, IFI27, IFI6, IFIT5, MX1 and TYK2) that were used to generate a score and were called the interferon signature.

Calculating the IFN score was important to capture a broad measure of the IFN-induced gene expression that would be less susceptible to fluctuations than a single gene assay. The z-score was used to calculate the type I IFN score for each subject. For each patient, a z-score was calculated for each gene by subtracting the healthy control mean value from the patient expression value for that gene and then dividing the difference by the healthy controls standard deviation (SD). The z-scores of the 6 genes were then added to produce a final component for each patient.

To optimize the specificity and sensitivity, an ROC curve was used to define the cutoff of the IFN signature. The accuracy (AUC), sensitivity (S), specificity (E), positive predictive value (PPV), negative predictive value (NPV) and confidence intervals were calculated.

2.3.4. Statistical analysis

Finally, the clinical and laboratorial features were analyzed to search for associations with the IFN signature. The continuous variables are expressed as the mean ± standard deviation (SD), and the categorical variables are presented in percentages. For the continuous

Table 1
Type I IFN genes known to be involved in the pathways related to the pathogenesis of SLE.

Gene ID	Abbreviation	Gene name
Hs01911452_s1	IFIT1	*Interferon-induced protein with tetratricopeptide repeats 1*
Hs00895608_m1	MX1	*Myxovirus resistance 1, interferon-inducible protein p78*
Hs00169345_m1	EIF2AK2	*Eukaryotic translation initiation factor 2-alpha kinase 2*
Hs01070332_m1	IFIH1	*Interferon induced with helicase C domain 1*
Hs01547283_m1	IRF3	*Interferon regulatory factor 3*
Hs00158114_m1	IRF5	*Interferon regulatory factor 5*
Hs01014809_g1	IRF7	*Interferon regulatory factor 7*
Hs00175238_m1	IRF8	*Interferon regulatory factor 8*
Hs00960941_m1	SULT1E1	*Sulfotransferase family 1E*
Hs00152844_m1	ELF1	*E74-like factor 1*
Hs00177464_m1	TYK2	*Tyrosine kinase 2*
Hs01018347_m1	IRAK1	*Interleukin-1 receptor-associated kinase 1*
Hs00234713_m1	TNFAIP3	*Tumor necrosis factor, alpha-induced protein 3*
Hs00374581_m1	TNIP1	*TNFAIP3 interacting protein 1 ABIN-1*
Hs00372523_m1	LRRC20	*Leucine rich repeat containing 20*
Hs00267809_m1	PTPRM	*Protein tyrosine phosphatase, receptor type, M PTPRL1*
Hs01013996_m1	STAT1	*Signal transducer and activator of transcription 1, 91kda*
Hs01063858_m1	IKBKE	*Inhibitor of kappa light polypeptide gene in B-cells, kinase epsilon*
Hs00174103_m1	IL8	*Interleukin 8*
Hs01058986_m1	RARRES3	*Retinoic acid receptor responder (tazarotene induced) 3*
Hs00737883_m1	IFNK	*Interferon kappa*
Hs01040689_m1	ANKS1A	*Ankyrin repeat and sterile alpha motif domain containing 1A*
Hs00748530_s1	UBE2L3	*Ubiquitin-conjugating enzyme E2L 3*
Hs00173500_m1	LPAR1	*Lysophosphatidic acid receptor 1*
Hs00324748_m1	PPM1H	*Protein phosphatase, Mg2+/Mn2+ dependent, 1H*
Hs00157342_m1	EFNA5	*Ephrin-A5*
Hs00204823_m1	VSIG2	*V-set and immunoglobulin domain containing 2*
Hs00176908_m1	PIK3C3	*Phosphatidylinositol 3-kinase, catalytic subunit type 3*
Hs00545621_m1	KLB	*Klotho beta*
Hs00158502_m1	KPNA1	*Karyopherin alpha 1 (importin alpha 5)*
Hs00266011_m1	DNAJA1	*Dnaj (Hsp40) homolog, subfamily A, member 1*
Hs01546665_m1	RPS6KA1	*Ribosomal protein S6 kinase, 90kda, polypeptide 1*
Hs01075861_m1	CD44	*CD44 molecule*
Hs00383235_m1	PTN	*Pleiotrophin1*
Hs01086373_g1	IFI27	*Interferon, alpha-inducible protein 27*
Hs00413458_m1	IFI35	*Interferon-induced protein 35*
Hs00951349_m1	IFI44	*Interferon-induced protein 44*
Hs00915292_m1	IFI44L	*Interferon-induced protein 44-like*
Hs00242571_m1	IFI6	*Interferon, alpha-inducible protein 6*
Hs00202721_m1	IFIT5	*Interferon-induced protein with tetratricopeptide repeats 5*
Hs00705137_s1	IFITM1	*Interferon induced transmembrane protein 1*

variables, the Mann-Whitney or Student's *t*-tests were used. For the categorical variables, Fisher's or Chi-square tests were used.

SPSS software and GraphPad Prism were used for statistics. All the tests were performed with a significance level of 5%.

3. Results

3.1. Demographic, clinical and laboratorial characteristics

From the total PAPS patient population (n = 53), 41 patients (77.4%) were women. The mean age of the patients at the assessment was 46.9 ± 10.9 years old, and the mean age at APS diagnosis was 31.6 ± 9.5. The APS patients had mean disease duration of 15.6 ± 7.1 years. The APS patients, healthy controls (HC) and positive controls (PC) were comparable with respect to age (respectively 46.9 ± 10.9 *vs.* 42.1 ± 15.5 *vs.* 51.7 ± 10.1; p = .08) and gender (77.4% *vs.* 72.3% *vs.* 68.9%, p = .83) (Table 2).

Table 2
Demographic, clinical and laboratorial characteristics.

	Primary APS (n = 53)	Healthy controls (n = 50)	Positive controls (n = 29)
Female (n,%)	41 (77.4%)	36 (72.3%)	20 (68.9%)
Age (mean ± SD)	46.9 ± 10.9	42.1 ± 15.5	51.7 ± 10.1
Age at diagnosis (mean ± SD)	31.6 ± 9.5	–	–
Disease duration (mean ± SD)	15.6 ± 7.1	–	–
aβ2GPI (IgM/IgG) (n,%)	28 (52.8)	0 (0)	0 (0)
Anticardiolipin (IgM/IgG) (n,%)	41 (77.3)	0 (0)	0 (0)
Lupus anticoagulant (n,%)	49 (92.4)	0 (0)	0 (0)
Triple positive (n,%)	25 (47.1)	0 (0)	0 (0)
ANA (n,%)	24 (45.2)	0 (0)	0 (0)
Anti-DNA (n,%)	0 (0)	–	–
Anti-Sm (n,%)	0 (0)	–	–
Anti-RNP (n,%)	1 (1.8)	–	–
Anti-SSA (n,%)	1 (1.8)	–	–
Anti-SSB (n,%)	0 (0)	–	–
Venous thrombosis (n,%)	38 (71.1)	–	–
Arterial thrombosis (n,%)	25 (47.1)	–	–
Arterial and venous thrombosis (n,%)	10 (18.8)	–	–
Pregnancy morbidity(n,%)	23 (43.4)	–	–
Thrombocytopenia (n,%)	12 (22.6)	–	–
Renal microangiopathy (n, %)	4 (7.5)	–	–
Heart Valve Disease (n,%)	2 (3.7)	–	–
Skin Ulcers (n,%)	5 (9.4)	–	–
Cognitive dysfunction (n, %)	10 (18.8)	–	–
Livedo (n,%)	17 (32.0)	–	–
Warfarin (n,%)	53 (100)	0 (0)	29 (100)
Aspirin (n,%)	4 (7.5)	0 (0)	1 (3.4)
Clopidogrel (n,%)	0 (0)	0 (0)	0 (0)
Statins (n,%)	15 (28.3)	0 (0)	8 (27.5)
LMWH (n,%)	1 (1.8)	0 (0)	1 (3.4)
DOACs (n,%)	0 (0)	0 (0)	0 (0)
Hydroxychloroquine (n, %)	28 (52.8)	0 (0)	0 (0)
Immunosuppressive drugs (n,%)	0 (0)	0 (0)	0 (0)
Prednisone (n,%)	0 (0)	0 (0)	0 (0)

APS: antiphospholipid syndrome, aβ2GPI: anti-β2-glycoprotein I, LMWH: low molecular weight heparin, ANA: anti-nuclear antibodies, RNP: ribonucleoproteins, SSA: Sjogren Syndrome A, SSB: Sjogren Syndrome B, DOAC: direct oral anticoagulants.

With respect to the aPL frequency in PAPS, LA was positive in 49 patients (92.4%), aβ_2GPI in 28 (52.8%) and aCL in 41 (77.3%). The frequency of triple aPL positivity was 47.1%. Although ANA was positive in 24 patients (45.2%), none of our patients had a positive anti-Sm or anti-DNA (Table 2).

All the selected APS patients had at least 1 thrombotic event, 38 (71.1%) had venous thrombosis, 25 (47.1%) had arterial thrombosis and 10 (18.8%) had both. Deep venous thrombosis and stroke were the most frequent events. Obstetric events were present in 23 (43.4%) patients. Noncriteria features were found in 31 (58.4%) patients, and of these, there was thrombocytopenia in 12 (22.6%), thrombotic microangiopathy in 4 (7.5%), skin ulcers in 5 (9.4%), heart valve disease in 2 (3.7%), cognitive dysfunction in 10 (18.8%), and livedo in 17 (32.0%) (Table 2).

All the PAPS patients were treated with warfarin 53 (100%), and only one patient was also receiving low molecular weight heparin due to an INR adjustment. None of our patients were taking new oral anticoagulants (NOACs). Four patients (7.5%) were taking aspirin concomitantly with warfarin, and none of these patients were using

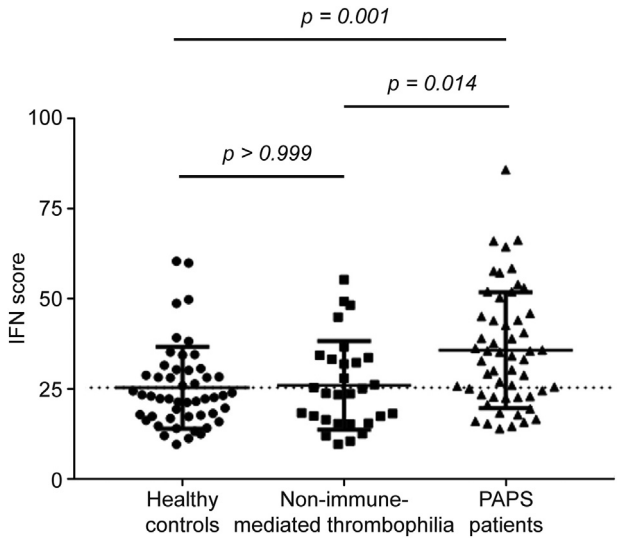
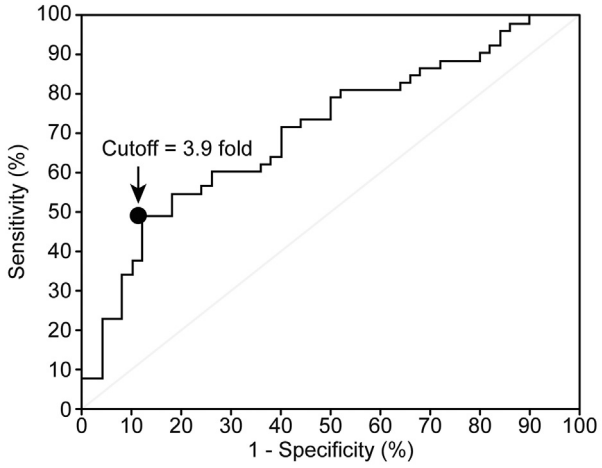


Fig. 1. Comparison of the IFN score of the PAPS patients, healthy controls and nonimmune-mediated thrombophilia patients.

clopidogrel. Twenty-eight patients (52.8%) were taking hydroxychloroquine, but none were using prednisone or immunosuppressive drugs (Table 2).

3.2. Increased IFN type I signature

With respect to the primary outcome, we concluded that 11 IFN-induced genes were highly expressed in PAPS. After the PCA analysis, 6 genes were chosen to compose the IFN signature: DNAJA1, IFI27, IFI6, IFIT5, MX1, and TYK2. The cutoff, determined by the ROC curve, was 3.9-fold (AUC = 0.706, S = 0.49, E = 0.86, PPV = 0.79, NPV = 0.61) (Figs. 1 and 2). The IFN signature was present in 49% of the PAPS patients, 14% of the healthy controls and 17% of the positive controls (p = .001) (Table 3).



Accuracy	p-value	CI (95%)
0.706	0.00031	0.606, 0.806

	%	CI (95%)
Sensitivity	49	36, 63
Specificity	86	76, 96
Positive predictive value	79	65, 93
Negative predictive value	61	50, 73

Fig. 2. Interferon Signature ROC Curve.

Table 3
Comparison of the primary APS patients with and without an IFN signature.

Characteristics	Type I IFN signature				p-value
	Absent		Present		
	N/Mean	%/SD	N/Mean	%/SD	
Age	49.5	11.2	44.2	10.2	0.079
Age at diagnosis	34.2	10.8	28.3	7.0	**0.023**
Disease duration	15.3	6.7	15.9	7.7	0.767
LA	27	100%	22	85%	0.051
aB2GPI	16	59%	12	46%	0.339
ACL	20	74%	21	81%	0.560
Triple positive	15	56%	10	38%	0.213
ANA	14	52%	10	38%	0.328
Venous thrombosis	19	70%	19	73%	0.827
Arterial thrombosis	13	48%	9	35%	0.406
Pregnancy morbidity	8	30%	15	58%	**0.039**
Abortion > 10 weeks	4	15%	8	31%	0.882
Abortion < 10 weeks	5	63%	7	47%	0.666
Prematurity	1	13%	5	33%	0.862
Preeclampsia	1	13%	8	53%	**0.032**
Renal microangiopathy	4	15%	2	8%	0.559
Thrombocytopenia	8	24%	4	20%	0.931
Heart valve disease	3	11%	1	4%	0.610
Skin Ulcers	0	0%	3	12%	0.111
Cognitive dysfunction	6	22%	6	23%	0.941
Livedo	7	26%	11	42%	0.208
Any noncriteria	15	56%	18	69%	0.305
Warfarin	27	100%	26	100%	0.983
Aspirin	2	7%	5	19%	0.250
Statins	13	48%	5	19%	**0.026**
Hydroxychloroquine	14	52%	17	65%	0.318

IFN: interferon, APS: antiphospholipid syndrome, aβ2GPI: anti-β_2-glycoprotein I, ANA: anti-nuclear antibodies.
Bold indicates p value < 0.05.

3.3. Comparisons between the patients with and without the IFN signature

The PAPS patients were divided in two groups according to the signature. Patients with and without an IFN signature were used to evaluate the possible associations with clinical and laboratorial features. All the comparisons are shown in Table 3.

A higher IFN signature was associated with a younger age at the first APS event (p = .023) and with the presence of obstetric events, especially with preeclampsia (p = .032).

There was no association between the IFN signature and the number of thrombotic events, laboratory exams, comorbidities, family history of autoimmune diseases, and thrombosis risk scores. Treatment with statins was associated a lower IFN score (p = .026).

4. Discussion

This study demonstrated that PAPS patients without lupus specific antibodies had an enhanced type I IFN gene signature that was not observed in nonimmune-mediated thrombophilia or in healthy controls.

Previously published studies show that an overexpression of IFN genes in primary APS is found in 20 to 28% of the patients with anti-dsDNA positive antibodies [16,17]. Although these patients did not have any lupus clinical features, it is known that anti-dsDNA antibodies can be present in the blood years before SLE diagnosis [22]. Therefore, the presence of a specific SLE antibody was defined as an exclusion criterion in our study.

Even with the exclusion of PAPS patients with positive SLE-specific antibodies, the prevalence of an IFN signature in the patients in this study was 49% (26/53), which was very similar to the previously reported prevalence of 46% (11/24) in another cohort [16]. As far as we know, this is the largest cohort that searched for an IFN signature in patients with primary APS, with 53 patients compared to 42 and 24 in

previous studies [16,17].

In this study, a third group of patients with nonimmune-mediated thrombophilia (the positive control group) who were all anticoagulated with vitamin K antagonists (the same treatment as patients with APS) was also included. In this third group, it was important to verify whether treatment with warfarin could in some way influence the signature of type I IFN. As expected, the expression of type I IFN in the positive control group was comparable to the healthy control group ($p = .94$), showing no influence of warfarin or the presence of previous thromboses on the IFN signature.

The present study also showed, for the first time, that the overexpression of genes regulated by type I IFN is associated with an earlier onset of APS events. This suggests that the IFN signature may predispose a patient to develop APS. This hypothesis explains, at least in part, the frequent association between APS and SLE (a disease where the known IFN signature is very relevant) [2,11]. Although it is generally known that inflammatory processes may act as second triggers in APS, the IFN signature has only been recently investigated [16,17].

Another interesting aspect revealed in this study was the association between the type I IFN signature and the occurrence of obstetric events, especially preeclampsia. In 2015, the same association was described in SLE patients [23]. In this study, higher levels of IFN-alpha were closely related to placental angiogenic dysregulation and the increased occurrence of preeclampsia [23].

In our cohort, the signature of IFN was not associated with the presence of ANA, lupus anticoagulant, anti-cardiolipin antibodies, aβ2GPI, triple positivity, or either the type or the number of thrombosis (arterial, venous or both). Accordingly, previous studies in PAPS also did not find any association between autoantibodies and the type I IFN signature [16,17].

Different from a previous publication that showed a lower IFN score in patients treated with hydroxychloroquine and statins [17], we only found an association between lower IFN signature levels and statin use, and no association was found with hydroxychloroquine. One possible explanation is that, in the present study, there was a greater percentage of patients taking HCQ (58% *vs.* 40.0%), which could influence the results [17].

We are aware of the limitations of this study. The reduced number of patients included (due to the rarity of the disease and strict inclusion criteria) and the cross-sectional design did not allow us to evaluate the behavior of the IFN signature during clinical events. It is noteworthy that longitudinal studies on the IFN signature in SLE failed to demonstrate an association between the IFN signature and disease activity. The signature is usually considered mainly a marker of severity and the type of organic involvement of SLE [13,15]. Probably, a personalized functional characterization of IFN pathways may provide further guidance for the selection of the most relevant therapeutic strategy in SLE [24] and this could also be useful for PAPS.

5. Conclusion

Our results indicate that PAPS patients without lupus specific antibodies have an enhanced type I IFN gene signature not observed in nonimmune-mediated thrombophilia. We also provide novel data demonstrating that this overexpression of type I IFN-regulated genes is associated with an earlier onset of APS events and preeclampsia. Further studies are necessary to determine if this subgroup of patients will benefit from interventions targeting the type I IFN signaling pathway.

Declarations of interest

None.

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