Universidade do Estado do Rio de Janeiro

Centro Biomédico

Faculdade de Ciências Médicas

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Manifestações oculares da síndrome do anticorpo antifosfolipídio

Rio de Janeiro

2023

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Tese apresentada, como requisito parcial para obtenção do título de Doutor, ao Programa de Pós-Graduação em Ciências Médicas, da Universidade do Estado do Rio de Janeiro.

Orientador: Prof. Dr. Flavio Mac Cord Medina

Coorientador: Prof. Dr. Flavio Signorelli

Rio de Janeiro

2023

CATALOGAÇÃO NA FONTE
UERJ/REDE SIRIUS/CBA

F825 Franco, Adriana Miranda de Magalhães.
Manifestações oculares da síndrome do anticorpo antifosfolipídio / Adriana Miranda de Magalhães Franco - 2023.
54 f.

Orientador: Prof. Dr. Flavio Mac Cord Medina
Coorientador: Prof. Dr. Flavio Victor Signorelli

Tese (Doutorado) – Universidade do Estado do Rio de Janeiro, Faculdade de Ciências Médicas.

1. Síndrome antifosfolipidica – Complicações – Teses. 2. Anticorpos Antifosfolipídeos. 3. Olhos – Doenças – Teses. 4. Amaurose fugaz. 5. Oclusão da artéria retiniana. 6. Retina – Doenças – Teses. I. Medina, Flavio Mac Cord. II. Signorelli, Flavio Victor. III. Universidade do Estado do Rio de Janeiro. Faculdade de Ciências Médicas. IV. Título.

CDU 616.831-005.6:617.7

Bibliotecária: Diana Amado B. dos Santos CRB7/6171

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Assinatura Data

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Aprovada em 22 de junho de 2022.

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Rio de Janeiro
2023

AGRADECIMENTOS

À minha sogra, Nelma de Abreu Feres, por compartilhar o meu sonho.

A meu marido, Maurício de Abreu Feres, pela paciência por todo o meu percurso.

À minha mãe, Maria Helena Pereira Miranda de Magalhães Franco, pelo carinho desde o início.

Aos meus orientadores, pelo acolhimento.

Aos amigos e médicos, Elaine Sobral da Costa, Márcia F. Demambro e Francisco Andrade, pelo estímulo.

A todo corpo de enfermagem e funcionários do Hospital Universitário Pedro Ernesto, que tornaram possível o meu projeto.

RESUMO

FRANCO, Adriana Miranda de Magalhães. **Manifestações oculares da síndrome do anticorpo antifosfolipídio**. 2023. 54 f. Tese (Doutorado em Ciências Médicas) – Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2023.

A Síndrome do anticorpo do Antifosfolípio (SAF) é uma síndrome rara, imunomediada, caracterizada pela presença de um ou mais episódios de trombose arterial e/ou venosa e/ ou de pequenos vasos e/ou critérios de morbidade gestacional, associados com a positividade dos anticorpos antifosfolipídios (aPL). Os objetivos deste estudo foram a avaliação em uma coorte de pacientes portadores de Síndrome de Antifosfolipídio Primária (SAFP) as manifestações oculares e comparar com grupo controle saudável, caracterizar a correlação das manifestações critério e não critérios com anticorpos antifosfolipídios (aPL) e realizar revisão sistemática da literatura. Foi realizado em duas etapas: na primeira (primeiro artigo), 105 pacientes foram avaliados em relação às manifestações oftalmológicas através da análise retrospectiva de prontuários e por entrevista incluindo sintomatologia ocular, além de revisão sistemática da literatura das manifestações oculares em pacientes portadores de SAFP ou portadores de aPL. Nesta etapa, tivemos diagnóstico oftalmológico em sete pacientes, com cinco oclusões de vasos retinianos. A amaurose fugax foi o sintoma mais comum, encontrado em 30 pacientes, estando relacionado na análise univariada a fenômeno de Raynaud ($p<0,048$), anticorpo anticardiolipina ($p<0,041$) e a hemianopsia relacionada com hipertensão arterial ($p<0,049$). Na multivariada foi encontrada associação de livedo reticular com amaurose fugax ($p<0,006$). Na revisão sistemática foram incluídos 96 artigos, incluindo achados do segmento anterior, posterior, orbitários e neuro oftalmológicos. Na segunda etapa (segundo artigo), realizamos um estudo transversal com 98 pacientes portadores de SAFP e 102 controles. Oitenta e quatro pacientes SAFP apresentaram alguma manifestação oftalmológica (94.0% achados no segmento posterior, 62.7% no segmento anterior e 56.6% apresentaram achados em ambos segmentos). A tortuosidade vascular foi mais frequente no grupo SAFP (63.2% vs. 42.2%; $p=0.002$), assim como a tortuosidade periférica (29.6% vs. 7.8%; $p<0.001$). Depois de excluídos os fatores de risco para ateroesclerose, a tortuosidade periférica permaneceu estatisticamente associada à SAFP (35.0 vs. 7.8%, $p<0.001$). Já a tripla positividade foi relacionada em pacientes SAFP com tortuosidade periférica e não foi relacionada nos pacientes SAFP sem esse achado ocular (34.5% vs. 15.9%, $p=0.041$). Dessa forma, devido à correlação com fenômeno de Raynaud e livedo, o primeiro estudo sugere a provável fisiopatologia vasomotora da amaurose fugax na SAFP. Além disso, o segundo estudo sugere que a tortuosidade periférica pode ser um marcador de retinopatia isquêmica, estando mais presente no fenótipo sorológico mais grave (triplo positivos).

Palavras-chave: Síndrome antifosfolipídica. Anticorpos antifosfolípides. Oftalmologia. Doenças oculares. Amaurose fugaz. Oclusão da artéria retiniana. Oclusão da veia retiniana. Cegueira monocular transitória.

ABSTRACT

FRANCO, Adriana Miranda de Magalhães. **Ophthalmological manifestations in primary antiphospholipid syndrome**. 2023. 54 f. Tese (Doutorado em Ciências Médicas) – Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2023.

Antiphospholipid antibody syndrome (APS) is a rare, immune-mediated syndrome characterized by the presence of one or more episodes of arterial and/or venous and/or small vessel thrombosis and/or criteria of gestational morbidity, associated with the positivity of the antiphospholipid antibodies (aPL). The objectives of this study were to evaluate ocular manifestations in a cohort of patients with Primary Antiphospholipid Syndrome (PAS) and compare them with a healthy control group, to characterize the correlation of criteria and non-criteria manifestations with antiphospholipid antibodies (aPL) and to carry out a systematic review of literature. It was performed in two stages: in the first (first article), 105 patients were evaluated in relation to ophthalmological manifestations through retrospective analysis of medical records and by interview including ocular symptomatology, in addition to systematic review of the literature on ocular manifestations in patients with PAPS or with antiphospholipid antibodies (aPL). At this stage, we had an ophthalmological diagnosis in seven patients, with five occlusions of retinal vessels. Amaurosis fugax was the most common symptom, found in 30 patients, being related in the univariate analysis to Raynaud's phenomenon ($p<0.048$), anticardiolipin antibody ($p<0.041$) and hemianopsia related to arterial hypertension ($p<0.049$). In the multivariate analysis, an association between livedo reticularis and amaurosis fugax was found ($p<0.006$). In the systematic review, 96 articles were included, including anterior, posterior, orbital and neuro-ophthalmological findings. In the second stage (second article), we conducted a cross-sectional study with 98 patients with PAPS and 102 controls. Participants underwent anamnesis and ophthalmological evaluation. Eight-four PAPS patients had some ophthalmological manifestation (94.0% found in the posterior segment, 62.7% in the anterior segment and 56.6% had findings in both segments. Vascular tortuosity was more frequent in the SAFP group (63.2% vs. 42.2%; $p=0.002$), as well as peripheral tortuosity (29.6% vs. 7.8%; $p<0.001$). After excluding risk factors for atherosclerosis, peripheral tortuosity remained statistically associated with APS (35.0 vs. 7.8%, $p<0.001$). Furthermore, the triple positivity was related in PAPS patients with peripheral tortuosity and was not related in PAPS patients without this ocular finding (34.5% vs. 15.9%, $p=0.041$). Thus, due to the correlation with Raynaud's phenomenon and livedo, the first study suggests the probable vasomotor pathophysiology of amaurosis fugax in PAPS. In addition, the second study suggests that peripheral tortuosity may be a marker of ischemic retinopathy, being more present in the most severe serological phenotype (triple positives).

Keywords: Antiphospholipid antibodies. Antiphospholipid syndrome. Ophthalmology. Eye disease. Retinal vein thrombosis. Retinal artery occlusions. Transient monocular blindness. Amaurosis fugax.

LISTA DE ABREVIATURAS E SIGLAS

aβ2GPI	Anti-β2 glicoproteína
aCL	Anticorpo anti cardiolipina
aPL	Anticorpo antifosfolipídio
APS-RIO	Síndrome do Anticorpo Antifosfolipídio Rio
HUPE	Hospital Universitário Pedro Ernesto
LAC	Anticoagulante Lúpico
LES	Lupus Eritematoso Sistêmico
SAF	Síndrome do Anticorpo Antifosfolipídio
SD-OCT	*Spectral Domain Technology*

SUMÁRIO

INTRODUÇÃO

A Síndrome do Anticorpo Antifosfolípídio (SAF) é uma doença rara, imunomediada, caracterizada por uma hipercoagubilidade adquirida[1], quando houver pelo menos um episódio de trombose arterial ou venosa de qualquer tecido ou órgão, confirmados por exame de imagem e/ ou exame histopatológico [1,2]. Se esta última confirmação for necessária, a trombose deve estar presente sem evidências de vasculite[2], embora a ativação de células endoteliais, monócitos, neutrófilos e mediadores inflamatórios estejam associados à patogênese da doença [3,4].

As manifestações obstétricas podem estar associadas ou não às manifestações trombóticas mencionadas acima e podem compreender um ou mais episódios de mortes de feto morfologicamente normal com 10 ou mais semanas de gestação; 1 ou mais partos prematuros de neonatos morfologicamente normais antes da 34º semana de gestação devido a eclampsia ou pré-eclampsia ou por insuficiência placentária e finalmente, três ou mais abortos consecutivos com menos de 10 semanas de gestação, desde que anormalidades cromossomiais tenham sido excluídas[2].

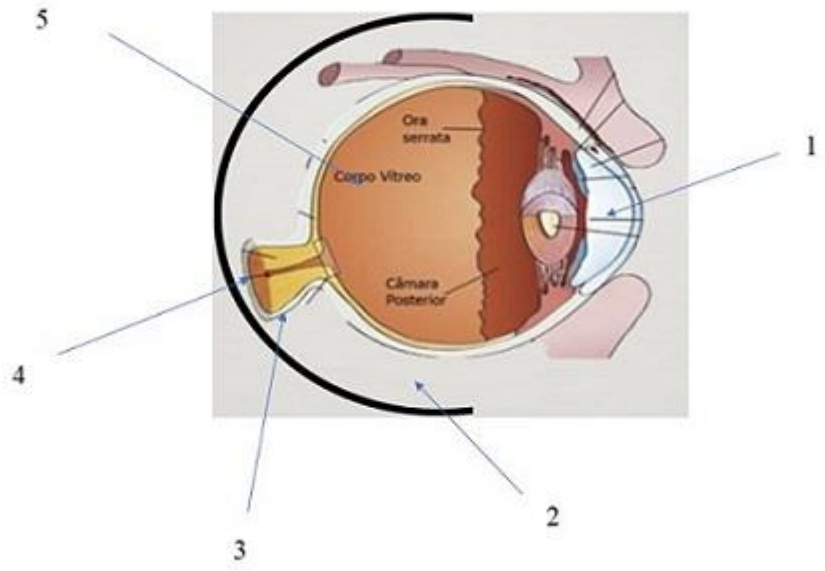
As manifestações trombóticas e/ ou obstétricas devem estar associadas à presença de anticorpos antifosfolipídios (aPLs) em duas ou mais ocasiões, com pelo menos 12 semanas de intervalo e menos de cinco anos de intervalo das manifestações clínicas e incluem a positividade do anticoagulante lúpico (LAC), presença de títulos médio-altos de IgM ou IgG anticorpo anticardiolipina (aCL) ou presença de IgM ou IgG anti-β2-glicoproteina 1(aβ2GPI) acima do percentil 99th [2-7].

Existem manifestações que segundo o último consenso[2], não são específicas para a SAF, mas cuja presença é muito frequentemente associada a mesma, sendo consideradas "não critério"[2] requerendo acompanhamento[8], como a trombose de veia superficial, trombocitopenia, microangiopatia renal, doença valvular cardíaca, *livedo reticularis*, enxaqueca, convulsões e mielite[9,10].

Aproximadamente 1% dos pacientes desenvolvem a apresentação mais grave da doença, a SAF Catastrófica, caracterizada por múltiplas tromboses na forma de microangiopatia trombótica, acometendo três ou mais órgãos ou sistemas, em um curto período de tempo, geralmente em uma semana com confirmação histopatológica de múltiplas oclusões de pequenos vasos, com mortalidade de até 50% dos casos [11,12].

As manifestações oftalmológicas trombóticas e não trombóticas podem ser a apresentação inicial da doença [13-15]. A Figura 1 e o Quadro1 ilustram os acometimentos oculares relacionados às estruturas.

Figura 1 – Anatomia do olho



Fonte: Adaptada de Malhotra et al.[16].

Quadro 1 – Segmento do Olho x Manifestações Oculares Relacionadas à SAF encontradas na nossa revisão x Anticorpos (Continua)

Segmento do Olho	Manifestações Oculares Relacionadas à SAF	Anticorpos
1- Anterior	Microaneurismas, telangectasisas, epiesclerite, esclerite, uveíte, anterior, uveíte hipertensiva, ceratite estromal e limbar, olho seco, catarata	aCL LAC
2- Órbita	Celulite pré septal, miosite orbitária, trombose de veia oftálmica superior, proptose, necrose de tecido orbitário	aβ2GPI; LAC; aCL;
3- Glaucoma e trabeculectomia	Glaucoma de ângulo aberto, glaucoma de pressão normal, glaucoma neovascular, glaucoma pseudoexfoliativo e síndrome pseudoexfoliativa	aβ2GPI; LAC; aCL; anticorpos antifosfatidil serina

Quadro 1 – Segmento do Olho x Manifestações Oculares Relacionadas à SAF encontradas na nossa revisão x Anticorpos (conclusão)

Segmento do Olho	Manifestações Oculares Relacionadas à SAF	Anticorpos
4- Glaucoma e trabeculectomia	Glaucoma de ângulo aberto, glaucoma de pressão normal, glaucoma neovascular, glaucoma pseudoexfoliativo e síndrome pseudoexfoliativa	aβ2GPI; LAC; aCL; anticorpos antifosfatidil serina
5- Neuro oftalmológicos	Amaurose fugaz; neuropatia óptica isquêmica não arterítica; neurite retrobulbar; hemianopsia homônima; quadrantopsia homônima; paralisia de pares cranianos e papiledema	aβ2GPI; LAC; aCL; anticorpos antifosfatidil serina
6- Posterior	Tortuosidade vascular difusa e periférica; obstrução de veia/ artéria retiniana, hemorragia vítrea e intra retiniana, edema macular, neovascularização, oclusão dos vasos coroidais; membrana neovascular sub retiniana, vasculite, estase venosa retiniana, coroidopatia serosa central, coroidite serpinginosa, retinopatia diabética, lesão da corio capilar e epitélio pigmentar, isquemia do plexo capilar profundo, descolamento de retina	aβ2GPI; LAC; aCL; anticorpos antifosfatidil serina

Legenda: Síndrome do Anticorpo Antifosfolípídio (SAF).
Fonte: A autora, 2023.

1 **OBJETIVOS**

1.1 **Geral**

Analisar as manifestações oftalmológicas em população bem definida de pacientes portadores de Síndrome do Anticorpo Antifosfolipídio Primária (SAFP), acompanhados no serviço de reumatologia do Hospital Universitário Pedro Ernesto (HUPE)/Universidade do Estado do Rio de Janeiro (UERJ) e comparar com um grupo de controle saudável.

1.2 **Específicos**

Os objetivos específicos são:

a) correlacionar as manifestações oculares com as manifestações critério e não critério e identificar se existe associação entre os eventos em pacientes portadores de SAFP;
b) correlacionar as manifestações oftalmológicas com a presença de anticorpos específicos da SAF; e
c) realizar revisão sistemática da literatura buscando associação de manifestações oftalmológicas com a SAFP ou de anticorpos específicos para SAF, sem a presença de Lupus eritematoso sistêmico (LES).

2 **JUSTIFICATIVA**

As manifestações oculares da SAFP são pouco descritas na literatura se resumindo a poucos estudos transversais e prospectivos, sendo a maioria relato de casos. Devido ao amplo espectro de acometimento oftalmológico e da gravidade de alguma delas torna-se necessário o estudo aprofundado dessas manifestações, das correlações destas com anticorpos antifosfolipídios e com manifestações critério e não critério, além das variáveis clínicas e laboratoriais associadas aos eventos.

3 **MATERIAIS E MÉTODOS**

Este estudo foi constituído de duas partes. A primeira parte (primeiro artigo), foi dividida em dois modelos. No primeiro modelo foi realizada revisão de prontuário à procura das manifestações oculares relacionadas à SAFP, anamnese para detecção dos sintomas oculares, além da correlação estatística com manifestações critério, não critério e com os aPLs. No segundo modelo foi realizada revisão sistemática da literatura à procura de artigos relacionados às manifestações oculares da SAFP ou de artigos com achados oftalmológicos com a presença de positividade para aPLs, sem a presença de outras doenças auto imunes.

A segunda parte foi realizada avaliação oftalmológica e anamnese minuciosa nos pacientes portadores de SAFP e em grupo controle saudável. O grupo controle foi selecionado entre funcionários do Hospital Universitário Pedro Ernesto, amigos e familiares destes. Neste grupo tentou-se excluir fatores de risco para ateroesclerose, como hipertensão, diabetes, dislipidemia, tabagismo e mulheres que tivessem feito uso de estrogênio até seis meses antes. A triagem foi realizada inicialmente por entrevista e envio e exames por *whatsapp*.

Os pacientes portadores de SAFP e os controles foram submetidos igualmente a anamnese, avaliação oftalmológica, além da documentação por retinografia do segmento anterior e posterior. Os exames de angiografia e avaliação do padrão macular pelo exame de tomografia de coerência óptica (OCT) foram realizados somente no grupo SAFP.

A avaliação das retinografias do segmento anterior e posterior do grupo SAFP e controle, tiveram as identificações retiradas, foram agrupadas por década de vida e por sexo e foram avaliadas por dois oftalmologistas “cegos”. Os exames de angiografia e OCT foram avaliados por dois oftalmologistas no padrão “não cego”, já que somente os pacientes SAFP realizaram estes exames.

O padrão de concordância entre os examinadores foi demonstrado através do coeficiente e teste Kappa.

A metodologia encontra-se detalhada em cada artigo do estudo.

4 ARTIGOS

4.1 Artigo 1 - Ophthalmologic manifestations in primary antiphospholipid syndrome patients: A cross-sectional analysis of a primary antiphospholipid syndrome cohort (APS-Rio) and systematic review of the literature (Artigo publicado)

Paper

Lupus
0(0) 1–16
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DOI: 10.1177/0961203320949667
journals.sagepub.com/home/lup
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Ophthalmologic manifestations in primary antiphospholipid syndrome patients: A cross-sectional analysis of a primary antiphospholipid syndrome cohort (APS-Rio) and systematic review of the literature

Adriana M de M Franco[1,2], Flavio Mac Cord Medina[2], Gustavo Guimarães Moreira Balbi[3], Roger Abramino Levy[1] and Flavio Signorelli[1,4]

Abstract

Objective: There is a broad spectrum of eye involvement in antiphospholipid syndrome (APS). The majority of descriptions are presented as case reports that include mostly APS patients secondary to systemic lupus erythematosus (SLE), with no compelling evidence in primary APS (PAPS). This study aimed to describe ocular manifestations in our well-defined PAPS cohort (APS-Rio) and then perform a systematic literature review (SLR) of ocular manifestations in patients with APS or positivity to aPL without SLE.

Methods: We retrospectively analyzed PAPS patients followed at our outpatient clinics. All patients fulfilled Sydney APS classification criteria (2006). We evaluated them for ocular symptoms and previous ocular diagnoses. Antiphospholipid antibodies and clinical APS manifestations were compared between patients with and without ocular manifestations. For the SLR, electronic databases were searched up to November 2019.

Results: We studied 105 PAPS patients; 90.5% were female and 56.2% were Caucasian. We found ocular manifestations in 37.1% of our cohort. Thrombosis was the main criteria manifestation (95.2%) and lupus anticoagulant was the most prevalent antibody. Ophthalmologic diagnoses were present in 7 patients, with 5 having retinal vessels thromboses. Amaurosis fugax was the leading complaint, present in 30 patients. In the univariate analysis, amaurosis fugax was related to livedo ($p = 0.005$), Raynaud's phenomenon ($p = 0.048$) and the presence of anticardiolipin antibody ($\geq$40 GPL/MPL) ($p = 0.041$). Hemianopia was associated with arterial hypertension ($p = 0.049$). In the multivariate analysis, the only association found was between livedo and amaurosis fugax (OR 4.09, 95%CI 1.5–11.11, $p = 0.006$). Our SLR incorporated 96 articles of ocular manifestations in patients with PAPS or positivity to aPL without SLE. Ocular findings varied from 5 to 88%, including anterior and posterior segments, orbital and neuro-ophthalmologic changes.

Conclusion: There is little evidence on ocular manifestations in PAPS. We described an association between livedo and amaurosis fugax. Prospective studies are needed to promote the best treatment and avoid blindness in PAPS patients.

Keywords

Antiphospholipid syndrome, antiphospholipid antibodies, thrombosis, eye disease, eye disorder, retinal diseases

Date received: 6 April 2020; accepted: 23 July 2020

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Introduction

Antiphospholipid syndrome (APS) is an acquired, autoimmune thrombophilia characterized by venous or arterial thrombosis and/or pregnancy morbidity in the presence of persistent serum antiphospholipid antibodies (aPL), tested on two or more occasions at least 12 weeks apart.[1–9] Laboratory criteria include positivity to lupus anticoagulant (LA), presence of IgM or IgG anticardiolipins (aCL) in moderate to high titers and presence of IgM and IgG anti-β2glycoprotein I (aβ2GPI) above the 99th percentile. Studies have demonstrated that patients with multiple positive test results display a much higher risk for developing clinical complications.[4,9–14] APS is classified when at least one clinical and one laboratory criterion is present.

Many non-criteria manifestations have also been described in APS. Understanding their prevalence may impact prognosis and morbidity.[15] There are few studies about ophthalmological manifestations in APS, most of them are limited to case reports or case series. Furthermore, many of them do not include patients with only primary APS (PAPS).

Ocular changes can be found in 8-88% of APS patients.[16] Manifestations are mainly due to thrombotic ocular events in central retinal vessels, but non-thrombotic ocular changes can also happen, even as the initial manifestation.[10]

This study aimed to describe ocular manifestations in our well-defined PAPS cohort (APS-Rio) and to perform a systematic literature review (SLR) of ocular manifestations in patients with APS or positivity to aPL without SLE.

Material and methods

Our study was divided in two parts. First, we conducted a cross sectional study in our PAPS cohort named APS-Rio, with initially 121 patients, from October 2015 to October 2019. All patients were clinically diagnosed and classified (Sydney criteria) as PAPS.[2] In this part, exclusion criteria were: other diagnosed autoimmune disease during screening or follow-up, positivity to aPL without criteria manifestations of APS, loss to follow-up and incapacity to answer the questions properly (for example, severe cognitive impairment).

Ocular manifestations were recorded by interview and chart review. Ophthalmologic examination was not performed at the time of analysis. We studied 2 different models: the first included objective findings and diagnosis of ocular manifestations, such as scleritis, neuritis, papilledema and thrombosis of ophthalmic main vessels and branches. The second included symptoms described during interview, especially amaurosis fugax, (defined as sudden monocular vision loss that can last between 2 to 30 minutes and can involve the entire visual field. It is also described as a "curtain coming down" in front of their eye or a generalized darkening or shadow, spontaneously resolved);[17,18] hemianopia (defined as loss of an entire hemifield of vision) or other partial vision deficit;[19] amaurosis (defined as completely loss of vision with no recovery and no perception of light)[20] and headache with scotomas (defined as headache without motor weakness and with reversible visual symptoms that can include flickering lights, spots or lines with no visual loss).[21] We excluded dry eye because many of them were using medications that could justify these symptoms.

We compared our patients with and without ocular manifestations in the 2 models based on demographic variables (considering sex, age, ethnicity and time elapsed since the first criteria manifestation), thrombotic and obstetrical criteria, criteria aPL, atherosclerosis risk factors (hypertension, dyslipidemia, diabetes, smoking and obesity) and non-criteria manifestations (valvulopathy, nephropathy, thrombocytopenia, livedo reticularis, Raynaud's phenomenon and migraine). Laboratory criteria included 2 or more positive aPL assays at least 12 weeks apart, including: LA, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (ISTH); IgG and/or IgM aCL in serum or plasma, present in medium or high titer (>40 GPL or MPL, measured by standardized ELISA); and IgG and/or IgM aβ2GPI (>99th percentile, measured by standardized ELISA).

Statistical analysis was performed using SPSS Version 22 (Chicago, Illinois). Categorical variables were presented as numbers and percentages and were analyzed by x^2 or two-tailed Fisher's exact test. Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range. Normality was analyzed by the Kolmogorov-Smirnov test. Student's T test was used for normally distributed continuous variables and Mann–Whitney-U test for asymmetrical continuous variables. Multivariate analysis was also performed when feasible and it was adjusted for age, sex and variables with $p < 0.10$ in univariate analysis. A p-value of <0.05 was considered as statistically significant.

Second, we conducted a SLR of ophthalmological manifestations in both PAPS and aPL positive patients without SLE. We used the PICo strategy for qualitative studies, as follows: Patients – primary antiphospholipid syndrome or patients positive to aPL without SLE; Interest – ocular manifestations; Context – any. All types of studies were included in our analysis.

PubMed, Scopus, Web of Science, Virtual Health Library (BVS) and Cochrane Library databases were searched up until November 21st, 2019, using the

following keywords: **"Antiphospholipid Syndrome"** (OR "Syndrome, Antiphospholipid" OR "Hughes Syndrome" OR "Antiphospholipid Antibody Syndr ome" OR "Antiphospholipid Antibody Syndromes" OR "Anti-Phospholipid Antibody Syndrome" OR "Anti Phospholipid Antibody Syndrome" OR "Syndrome, Anti-Phospholipid Antibody" OR "Anti-Phospholipid Syndrome" OR "Anti Phospholipid Syndrome" OR "Antiphospholipid Antibodies" OR "APS"), **"Beta 2-Glycoprotein I"** (OR "Beta 2 Glycoprotein I" OR "Apo H" OR "Endothelial Cell-Viability Maintaining Factor" OR "Endothelial Cell Viability Maintaining Factor" OR "Beta^{2}GPI" OR "Beta2-Glycoprotein I" OR "Beta2 Glycoprotein I" OR "EC-VMFa" OR "EC VMFa" OR "Anticardiolipin Cofactor" OR "Apolipoprotein H"), "**Anticardiolipin Antibodies**" (OR "Anticardiolipin Antibody" OR "Anticardiolipin" OR "Antibody, Anticardiolipin"), "**Lupus Anticoagulant**" (OR "Lupus Coagulation Inhibitor"), AND **"Eye Manifestations"** (OR "eye manifestation", "Ocular vaso occlusive disease" OR "ocular manifestations" OR "ocular manifestation" OR "ocular disease" OR "ocular involvement" OR "ocular symptoms" OR "ocular features"), **"Amaurosis Fugax"** (OR "Blindness, Monocular, Transient" OR "Blindness, Transient Monocular" OR "Monocular Blindness, Transient" OR "Transient Monocular Blindness"), **"Retinal Vein Occlusion"** (OR "retinal vein occlusions" OR "retinal vein thrombosis" OR "retinal vein thromboses" OR "vein thrombosis, retinal"), "**Retinal Artery Obstruction**" (OR "retinal artery occlusion" OR "retinal artery thrombosis" OR "retinal thrombosis" OR "ocular arterial" OR "retinal vascular occlusions"), **Uveitis**, **Scleritis, Episcleritis**, **Diplopia** (OR diplopias OR "double vision" OR "vision, double" OR polyopsia OR polyopsias OR polyopsis), **Hemianopia** (OR hemianopsias OR hemianopsia OR hemianopias), **quadrantanopia** (OR quadrantanopsias OR quadrantanopsia OR quadrantanopias), "**Sjogren's Syndrome"** (OR "sjogrens syndrome" OR "syndrome, sjogren's" OR "sjogren syndrome" OR "sicca syndrome" OR "syndrome, sicca" OR "dry eye") and "**Visual Disturbances**".

The highly sensitive search strategy was performed, and data was analyzed and reported according to PRISMA guidelines with no time restrictions around the year of publication. Most selected articles were in English, except for 1 in Russian, 1 in German, 2 in French, and 1 in Portuguese. Initially, we identified 2284 articles and inserted 29 publications manually. We then excluded 1062 overlapping retrieved articles. Of the 1251 papers remaining, 1004 were excluded based on the title and 81 based on the abstract. After that, 166 were selected for reading, but 13 were excluded since full-text was not available even after trying to contact the corresponding author. Fifty-seven were excluded because they were not related to ophthalmological manifestations in primary antiphospholipid syndrome or aPL positivity in the absence of SLE. Finally, 96 papers were included in the qualitative analysis (59 case reports, 7 case series, 7 cross-sectional studies, 5 case-control studies, 9 prospective studies and 9 systematic reviews). All studies were observational. Findings were classified according to the ocular segment analyzed. The PRISMA flowchart is presented in Figure 1.

Part I – Ophthalmologic findings in our cohort (APS-Rio)

Results

From the initially screened patients (N = 121), 2 were excluded due to severe cognitive impairment after stroke and 14 patients were lost to follow-up, leaving 105 patients for the analysis. Ninety-five patients (90.5%) were female and 59 (56.2%) were Caucasian. Thrombotic PAPS was the main criteria manifestation (95.2%); 77.3% had venous and 41.9% had arterial thrombosis. Obstetrical criteria were present in 39%. Lupus anticoagulant was the most prevalent antibody. The main characteristics of our population are shown in Table 1. In model 1, 6.7% of patients presented with objective findings or ophthalmologic diagnoses. These seven patients are described in detail in Table 2. On the other hand, in model 2, 38 patients (36.2%) had some ocular complaint, totalizing 61 symptoms. The most prevalent was amaurosis fugax, reported by 30 patients (78.9% of symptomatic patients), followed by diplopia in 13 patients (34.2% of symptomatic patients). Hemianopia and migraine with visual aura were found in 3 and 9 patients, respectively. Six patients had some permanent visual loss in at least one eye. The symptoms and their associations are shown in Table 3. Combining signs and symptoms, we found that 37.1% of patients in our population had ophthalmologic findings.

When we analyzed the first model, we could not find any statistical association, likely due to the low prevalence of specific events. Meanwhile, in model 2, univariate analysis showed that amaurosis fugax was related to livedo ($p = 0.005$), Raynaud's phenomenon ($p = 0.048$) and the presence of aCL $\geq$40MPL/GPL ($p = 0.041$). Hemianopia was associated with arterial hypertension ($p = 0.049$). In multivariate analysis, the only persistent association was livedo with amaurosis fugax (OR 4.09, CI 1.5–11.11, $p = 0.006$).

Table 1. General characteristics of APS-Rio cohort (N = 105).

Variable	Values
Age (mean ± standard deviation)	44.9 ± 12.1
Female (N, %)	95 (90.5%)
Caucasian (N, %)	59 (56.2%)
Time from first manifestation (mo) (median (interquartile range))	132 (84–228)
Arterial hypertension (N, %)	39 (37.1%)
Diabetes (N, %)	8 (7.6%)
Dislipidemia (N, %)	32 (26.7%)
BMI (kg/m^2) (median (interquartile range))	28.7 (25.1-32.9)
Smoking ever (N, %)	28 (30.5%)
Thrombocytopenia	9 (8.6%)
Valvulopathy*	8 (7.6%)
Nephropathy	1 (1%)
Livedo reticularis	25 (23.8%)
Migraine	53 (50.5%)
Raynaud's phenomenon	27 (25.7%)
Autoantibodies	
Lupus anticoagulant	99 (94.3%)
Anticardiolipin	36 (34.3%)
Anti-β2glycoprotein I	43 (41.0%)
Thrombotic APS	100 (95.2%)
Thrombotic + Obstetric APS	36 (34.3%)

Categorical variables are described as N (%); continuous variables are described as mean ± SD or mean (interquatile range). MO = months, BMI = body mass index. *N = 92.

related to APS.[78,79] Occlusion of choroidal vessels was reported to be associated with catastrophic APS.[80,81]

Findings mimicking serpiginous choroidopathy[82] and masquerading diabetic retinopathy[83] were described as manifestations of retinal and choroidal vascular occlusions in APS.

Arf et al.[84] reported a case of a female patient with sudden onset of decreased vision in the right eye, followed by progressive worsening six months later in both eyes. Spectral-domain optical coherence tomography (SD-OCT) showed a characteristic image of a hyperreflective band in the inner nuclear and inner plexiform layers in the acute stage, and thinning of these layers in the chronic stage. The authors related the event to diffuse retinal atrophy linked to widespread deep capillary plexus ischemia. Laboratory findings confirmed the diagnosis of APS.

Schofield et al.[85] presented a case series of three patients with sudden onset of focal paracentral scotoma and persistent presence of high-titers of prothrombin-associated antiphospholipid antibodies. SD-OCT revealed a bilateral disruption of outer nuclear and outer plexiform layers consistent with prior ischemia of the deep capillary plexus. In all of them, the optical coherence tomography angiography (OCT-A) also revealed focal deep capillary loss. The authors attributed the findings to APS.

Trese et al.[86] described a case of a paracentral acute middle maculopathy as a manifestation of PAPS in a 44-year-old male patient with sudden onset of a blind spot in his right eye and no known thrombotic risk factors. Fluorescein angiography demonstrated a slightly delayed arteriovenous transit time in the early phase and mild focal hypofluorescence corresponding to the lesion supratemporal to the optic nerve. SD-OCT identified several hyperreflective, band-like lesions located at the junction of the outer plexiform layer and inner nuclear layer that extended into the latter, representing ischemia of the deep retinal capillary plexuses. OCT-A demonstrated perfusion deficits at the level of superficial capillary plexus, deep capillary plexus and the choriocapillaris. Serial SD-OCT imaging showed thinning of the inner nuclear layer over time. Serologic testing revealed elevated aβ2GPI. There were no other laboratory diagnostic features associated with any other systemic disease, which led to diagnosis of PAPS.

Cicinelli et al.[87] published a case of 70-year-old woman presenting with progressive visual field restriction. Ultra-widefield fluorescein angiography showed non-perfusion and segmental perivascular leakage, more evident in the inferonasal quadrant veins. The posterior pole showed foveal avascular zone enlargement and scattered areas of ischemia within the vascular arcades. Laboratory tests showed repeated high aCL titers, both IgM and IgG, which confirmed the diagnosis of PAPS (other autoimmune disorders were ruled out). Finally, ocular APS may manifest as a severe occlusive peripheral microangiopathy in rare occasions, leading to diffuse capillary non-perfusion and small arteriolar obliteration.[87]

Orbital changes

Preseptal cellulitis with recurrent non-healing and non-infectious ulcer[88] and orbital myositis[89] were reported as unusual presentations of APS. Dey et al.[90] described acute proptosis and ophthalmoplegia due to superior ophthalmic vein thrombosis as initial manifestation of APS.

Ocular manifestations of catastrophic APS also include bilateral ophthalmoparesis, proptosis, increased intraocular pressure and necrosis of orbital tissue.[24,65,91]

Neuro-ophthalmic changes

Antiphospholipid antibodies can lead to a wide array of neuro-ophthalmological conditions, ranging from extra-ocular motility disturbance to central nervous

Table 2. Clinical and laboratory manifestations associated with ophthalmologic findings (Model 1).

Patient	Age at ocular manifestation	Ocular finding was the first manifestation?	Ocular finding	Criteria manifestations	Non-criteria manifestations	aPL
Patient 1 Female, Non-Caucasian	15	Yes	Central retinal artery and vein thrombosis in the right eye	Ocular thrombosis	Migraine	LA
Patient 2 Female, Caucasian	25	Yes	Optic neuritis in the right eye	Deep vein thrombosis in the left leg	Migraine Livedo reticuar	LA
Patient 3 Female, Caucasian	48	Yes	Central retinal vein thrombosis in the right eye, edema and papiledema in the left eye	Transient ischemic attack	Migraine Livedo racemosa Raynaud phenomenon Valvulopathy	LA
Patient 4 Female Non-Caucasian	35	Yes	Central retinal vein thrombosis in the left eye Conjuntival telangectasis	Ischemic stroke-Abortion Deep vein thrombosis in the right leg Thrombosis of the commom left carotid artery	Migraine	LA aβ2GPI
Patient 5 Female, Non-Caucasian	35	No	Central retinal artery thrombosis in the right eye Right retinal detachment	Deep vein thrombosis in the left leg Abortion	Migraine Amaurosis fugax Valvulopathy	LA aCL
Patient 6 Female, Non-Caucasian	51	No	Sscleritis	Four ischemic strokes	Migraine	aCL aβ2GPI
Patient 7 Female Caucasian	36	No	Papiledema	Thrombosis of both legs; internal jugular thrombosis	Migraine Seizures	LA

Note: aCL – anticardiolipin antibodies; aPL – antiphosphlipid antibodies; aß2GPI – anti-beta-2-glycoprotein I antibodies; LA – lupus anticoagulant.

Table 3. Clinical and laboratory manifestations associated with ophthalmologic manifestations (Model 2).

Ophtalmologic symptom	N (% of total)	Criteria manifestations (N – %)	Non criteria manifestations (N – %)	aPL associated (N – %)	Triple positivity (N – %)
Amaurosis fugax	30 (28.6%)	Venous Thrombosis (24–80%) Arterial Thrombosis (16–53.3%) Fetal Loss (7–23.3%) Prematurity (3–10%) Abortion (7–23.3%)	Migraine (18–60%) Raynaud Phenomenon (10–33.3%) Livedo (11–36.7%) Thrombocytopenia (3–10%)	LA (23–76.7%) aCL (8–26.7%) aβ2GPI (7–23.3%)	2 (6.7%)
Diplopia	13 (12.4%)	Venous Thrombosis (5–38.5%) Arterial Thrombosis (4–30.8%) Abortion (6–46.1%) Fetal loss (6–46.1%) Prematurity (3–23.1%)	Migraine (5–38.5%) Raynaud Phenomenon (5–38.5%) Livedo (5–38.5%)	LA (11–84.6%) aCL (4–30.8%) aβ2GPI (2–15.4%)	1 (7.7%)
Hemiamnopsia	3 (2.6%)	Venous Thrombosis (3–100%) Arterial thrombosis (1–33.3%) Abortion (2–66.7%) Fetal loss (1–33.3%)	Raynaud Phenomenon (2–66.7%) Livedo (2–66.7%)	LA (2–66.7%) aCL (1–33.3%)	0 (0)
Permanent visual deficit in at least one eye	4 (3.8%)	Venous Thrombosis (3–75%) Arterial thrombosis (3–75%) Abortion (2–50%) Fetal loss (1–25%)	Migraine (3–75%) Livedo (1–25%)	LA (4–100%) aCL (1–25%)	0 (0)
Migraine with visual aura	9 (8.6%)	Venous Thrombosis (6–66.7%) Arterial Thrombosis (6–66.7%) Fetal Loss (3–33.3%) Abortion (3–33.3%)	Migraine (4–44.4%) Valvulopathy (1–11.1%) Livedo (1–11.1%)	LA (4–44.4%) aCL (1–11.1%)	0 (0)

Note: aCL – anticardiolipin antibodies; aPL – antiphosphlipid antibodies; aß2GPI – anti-beta-2-glycoprotein I antibodies; LA – lupus anticoagulant; N – number of patients.

system infarctions of the visual pathway.[11,12] Multiple thromboses of small blood vessels that supply *fundus oculi* probably lead to demyelination and axon destruction in APS.[24]

Unilateral or bilateral transient vision loss (amaurosis fugax) is a frequent complaint, but in most cases, it has no pathological finding.[22,92–96]

Central nervous system infarctions along the visual pathway or visual cortex can explain the most common neuro-ophthalmic findings, including non-arteritic ischemic optic neuropathy,[7,24,96–98] retrobulbar optic neuritis,[99] homonymous hemianopia[100] and homonymous quadrantanopia.[101] Watts et al. [102] described a non-arteritic pattern in 12 out of 19 patients with anterior ischemic optical neuropathy and found that IgG aCL was statistically significantly related to this clinical presentation.

Abu el-Asrar et al. reported a case series of compression of the central retinal vein by a swollen optic nerve, predisposing patients to central retinal vein occlusion. Also, the presence of thrombophilic abnormalities may have contributed to the concomitant occlusion of posterior ciliary arteries and central retinal vein.[103]

Shin et al. described a single case of multiple cranial nerve palsies associated with papilledema secondary to idiopathic intracranial hypertension in an APS patient.[104]Ali et al. [105] reported a rare case of APS presenting as papilledema and sixth nerve palsy in the right eye due to superior sagittal sinus thrombosis, which ceased after anticoagulation and acetazolamide therapy. Champion et al.[106] described a 24-year-old female who presented with sudden onset of painless diplopia and ptosis in her left eye, with isolated incomplete pupil-sparing left oculomotor nerve palsy. Magnetic resonance imaging demonstrated focal hyperintensity in the left midbrain with infarction suggested by diffusion-weighted imaging. PAPS was diagnosed by the demonstration of positive LA, in the absence of other autoimmune disease.

Finally, electrophysiological activity of the retina was studied in APS patients, showing an abnormal electroretinography with consistently lower a- and b-wave amplitudes in 70% of cases and a decrease in the oscillatory potential in 82% of the patients, probably because of the retinal ischemia.[107]

Glaucoma and trabeculectomy

Neovascular glaucoma was described in association with retinal vascular occlusion (arterial or venous).[33,45]

Tsakiris et al.[108] tested LA, aCL and aβ2GPI in 22 patients with normal tension glaucoma, 23 patients with chronic open angle glaucoma and 25 control patients and found no statistically significant difference between groups.

On the other hand, the Canadian Glaucoma Study 3[109] analyzed rates of visual field change in 216 patients with glaucoma and evaluated risk factors for progression, including abnormal aCL level, age, female sex, and mean follow-up intraocular pressure (IOP). They found that patients with abnormal aCL levels and older age had faster visual field change, and modest IOP reduction in progressors correlated with slower rates of visual field worsening.

Research has shown that elevated serum aPL are more common in patients with pseudoexfoliation syndrome and pseudoexfoliation glaucoma than in healthy controls. There is also an association described between elevated aPL and primary open angle glaucoma.[110,111]

Januleviciene et al.[112] evaluated the effects of trabeculectomy on ocular hemodynamics parameters in 46 patients with pseudoexfoliative glaucoma or primary open glaucoma and analyzed serum aPL levels in pseudoexfoliative glaucoma. They found that IOP levels decreased significantly less in patients after trabeculectomy in pseudoexfoliative glaucoma than in primary open angle glaucoma. They also concluded that patients with undetectable aPL had a statistically significant increase in ocular hemodynamic parameters compared with patients with high titer aPL levels. They did not mention which aPL were tested.

IgG antiphosphatidyl-serine antibodies concentrations were significantly increased in normal tension glaucoma associated with hearing loss compared to normal tension glaucoma patients with normal audition or healthy controls.[113,114]

The segment of the eye and its association with different antibodies, are summarized in Table 4.

Discussion

Prevalence of ophthalmologic manifestations in PAPS varies widely, ranging from 5 to 88%.[26,27,32,36,115] Overall, we found ophthalmologic findings in 37.1% of our cohort.

Of the 96 studies included in the systematic review, only 3 observational studies (2 cross-sectional and one prospective) had a design similar to ours (i.e. evaluating ocular manifestations in patients with previous diagnosis of PAPS). All of them enrolled a limited number of patients. We conducted a cross-sectional study with 105 PAPS patients. The comparison between the studies is shown in Table 5.

In a prospective study, Miserocchi et al.[25] evaluated ocular features in 13 patients presenting with inflammation in the presence of aCL. Eye examinations were performed and clinical characteristics were divided into anterior and posterior segments. Ocular symptomatology was also obtained. In this study, one patient with SLE and another one with Whipple's disease were

Table 4. Summary of diseased part of the eye and their association with different antibodies, according to the systematic literature review.

Eye segment	Description*	Associated aPL
Anterior eye segment	Telangiectasia (1)	1 – aCL
References: 22–32	Microaneurysm (1)	2 – LA
	Dry eye (1,2)	
	Episcleritis (1)	
	Scleritis (1)	
	Filamentary, limbal keratitis (1)	
	Iritis (1,2)	
	Necrotizing scleritis (2)	
	Uveitis (1,2)	
Posterior eye segment	Venous tortuosity (1–3)	1 – aCL
References: 7,11,12,22,23–28,33–88	Central retinal vein occlusion (1–3)	2 – LA
	Branch retinal vein occlusion (1–3)	3 – aβ2GPI
	Central retinal artery occlusion (1,2)	4 – aPS
	Branch retinal artery occlusion (1–4)	5 – Not specified
	Venous stasis retinopathy (1,2)	
	Vitreous and intraretinal hemorrhages (1–3)	
	Subhyaloid hemorrhage (1–3)	
	Retinal vasculitis (1,3,4)	
	Vitritis (1,2)	
	Cotton wool spots (1–4)	
	Macular edema (1,2)	
	Neovascularization (1,2)	
	Exudate (1,2)	
	Diffuse retinal periphlebitis (1–3)	
	Choroidal infarction (1)	
	Unexplained choroidal embolization (1,2)	
	Choroidal neovascular membrane (5)	
	Damage of choriocapillaris and retinal pigmented epithelium (5)	
	Occlusion of choroidal vessels (1–3)	
	Central serous chorioretinopathy (1,2)	
	Serpiginous choroidopathy (1,2)	
	Ischemia of the deep capillary plexus (3,4)	
Orbital changes	Preseptal cellulitis (2)	
References: 24,66,89–92	Orbital myositis (1)	1 – aCL
	Superior ophthalmic vein thrombosis (2)	2 – LA
	Ophthalmoparesis (2)	3 – aβ2GPI
	Proptosis (2,3)	
	Necrosis of orbital tissue (1,3)	
Neuro-ophthalmologic changes	Amaurosis fugax (1,2,4)	1 – aCL
References: 7,11,12,22,24,93–108	Non-arteritic ischemic optic neuropathy (1–3)	2 – LA
	Retrobulbar optic neuritis (1–3)	3 – aβ2GPI
	Homonymous hemianopia (1–3)	4 – aPS
	Homonymous quadrantanopia (3)	
	Multiple cranial nerve palsies associated with papilledema (1,2)	
	Papilledema and sixth nerve palsy (2)	
	Isolated fascicular oculomotor nerve palsy (2)	
Glaucoma and trabeculectomy	Neovascular glaucoma (1)	1 – aCL
References: 34,46,109–115	Normal tension glaucoma (1–4)	2 – LA
	Open angle glaucoma (1,3)	3 – aβ2GPI
	Pseudoexfoliation syndrome (1)	4 – aPS
	Pseudoexfoliative glaucoma (1)	

Note: aß2GPI – anti-beta-2-glycoprotein I, aCL – anticardiolipin, LA – lupus anticoagulant, aPS – antiphosphaditilseryne antibodies.
*The numbers between brackets represent the associated aPL, which may be found in the following column.

Table 5. Continued.

Author	Design of the study	Number of patients	Anterior segment disease (N – %)	Posterior segment disease (N – %)	Neuro ophtalmic findings (N – %)
				(10–45.4%)	
				Posterior pole and/or peripheral pigment epithelial window defects in fluorescein angiography (7–31.8%)	
Our present study	Cross sectional	105	Scleritis (1–0.9%)	Retinal vein occlusion (4–3.8%)	Amaurosis fugax (30–28.6%)
				Retinal artery occlusion (2–1.9%)	Diplopia (13–12.4%)
				Retinal detachment (1–0.9%)	Hemianopsia (3–2.9%)
					Neuritis (2–1.9%)
					Papilledema (1–0.9%)
					Scleritis (1–0.9%)
					Central retinal artery occlusion (2–1.9%)
					Central vein thrombosis (2–1.9%)
					Retinal detachment (1–0.9%)
					Teleangectasia (1–0.9%)

included. In their findings, 8 patients presented with iritis, 2 with scleritis and 1 patient with keratitis, with anterior segment abnormalities present in 76% of patients. The most represented feature of posterior involvement was retinal vasculitis (60%), followed by vitritis (38%), retinal detachment (15%), posterior scleritis (7%), and central retinal artery occlusion (7%). In some papers,[11,12,18,19,62] both PAPS and secondary APS were included, so there were more ocular findings, such as cotton-wool spots, choroidal infarcts, serous macular detachment, and vitritis, which are also seen in other immunological diseases, especially SLE.

The anterior segment is rarely involved in PAPS. We had only one patient with scIeritis (patient 6). Anterior findings described in other studies were episcleritis, conjunctival microaneurysms/telangiectasia, rubeosis iridis and cataract associated with an absolute glaucoma.

The posterior segment is described as the most frequently affected. We identified six central retinal thromboses and one retinal detachment. In contrast, neuro-ophthalmic findings were more common than posterior segment in our study, represented by 30 patients with amaurosis fugax. This may be explained by the methodology focused in symptomatology and chart review.

Leo-Kottler et al.[116] conducted a retrospective study of 50 patients positive for aPL, two of them fullfilled criteria for SLE diagnosis and twenty-four patients (48%) also had positive thyroid antibodies. In this study, a combination of both transient and permanent visual disturbances was noted in 54% of the patients, with 20% being transient visual disturbances. Gelfand et al.[92] prospectively studied 39 PAPS patients; 33% had a combination of both transient and permanent visual disturbances. Ten patients had transient and 3 had permanent symptoms. The authors described, among the transient symptoms, 3 amaurosis fugax, 3 bilateral visual obscurations, 2 diplopia, 1 migraine with scintillating scotoma and 1 homonymous hemianopia. In patients presenting permanent symptoms 2 showed homonymous hemianopia and 1 dry eyes.[92] The study showed a 28.6% prevalence of transient and 5.7% of permanent visual loss.

Amaurosis fugax was related to livedo reticularis and Raynaud's phenomenon in our patients and, as far as we are aware, it is the first description of this finding in the literature. In the multivariate analysis, amaurosis fugax continued to be associated with livedo. Leo-Kottler et al.[116] found an association between amaurosis fugax in 50 patients with aPL positivity. Anti-thromboplastin antibodies and aCL antibodies were present in 46 and 36 patients, respectively. In our univariate analysis, amaurosis fugax was related to aCL antibodies.

Livedo reticularis has already been associated with arterial thrombosis in other sites (mainly stroke).[15,117] In histopathology analysis, however, identification of thrombi in livedo specimens is considered rare,[118] which reinforces the role of vasculopathy and vasospasm in its pathogenesis. Therefore, there are two mechanisms that may explain the association between livedo reticularis and amaurosis fugax: vasospasms due to an abnormal response secondary to vasculopathy (reinforced by the association with Raynaud's phenomenon in the univariate analysis) or transient thrombosis of the retinal vascular system. We believe vasculitis is not a plausible explanation for this finding, since most APS manifestations require the absence of vascular inflammatory infiltrates.[2] Even in livedoid vasculopathy, there is no clear histopathologic evidence of true vasculitis (inflammatory infiltrate or leukocytoclasia).[119]

Many studies, unlike ours, searched for APS diagnosis in patients with a specific ocular finding. Cobo-Soriano et al.[32] performed a prospective study with 40 patients with occlusive retinal disease, without thrombosis risk factors. They found 22.5% of aPL positivity, with aCL being the most common. Bashshur et al.[45] also described 24 patients with occlusive retinal disease without risk factors and found 10 patients positive for aCL and all of them negative for LA. Coniglio et al.[115] identified LA and/or aCL positivity in 33% of 48 patients with venous occlusive retinal disease, confirming APS diagnosis. A French study[120] that included patients with occlusion of retinal vein, found 9 out of 68 patients (13.2%) had positive aPL. Five of these 9 patients were positive for aCL IgG, 1 patient was positive for both aCL isotypes and aβ2GPI IgM, and the other three patients had two positive determinations for aβ2GPI IgM. On the other hand, a prospective study[36] with 75 patients with occlusive retinal vascular disorders were screened for aPL and compared with a control group. The authors could not demonstrate any statistical significance of aPL between the group showing occlusive retinal disease and the control group, even though one patient has LA and three patients had aCL positivity. Two case series[121,122] demonstrated that the aCL isotype IgM was specifically related to retinal thrombosis. A cross-sectional ophthalmologic study[26] of 17 PAPS patients showed 10 patients with visual symptoms and 15 patients with fundus abnormalities. aCL IgG was positive in all 17 patients and LA was positive in 4 patients.[26] Finally, Palmowski-Wolfe et al.[123] prospectively studied 368 patients with retinal vessels thrombosis. Their results showed that 86 (23.4%) of patients had aPL, mainly aCL. Nevertheless, when they excluded other thrombosis risk factors, only 15.3% of 85 patients had solely aPL positivity. Our study had LA predominance and aCL was the less frequent aPL. We could not find any association of retinal thrombosis and a specific aPL. This could reflect our low prevalence in only six patients (Table 5).

Our study has several limitations. First, it is a cross-sectional study and we could only suggest any association. Second, our methodology was based on interviews and chart review. We did not perform an ophthalmologic examination. The favorable aspects were the number of patients included (105 patients) and a restricted selection of only PAPS patients. We studied patients with previous PAPS diagnosis, while many studies started from ophthalmologic diagnosis.

In conclusion, we found amaurosis fugax as the most common ocular finding and it was related to vasomotor phenomena like Raynaud's phenomenon and livedo. Prospective studies are necessary to better understand the spectrum of ophthalmologic manifestations in PAPS, in order to better treat and avoid blindness in our patients.

Acknowledgements

We would like to thank Christine Henning, PharmD, Global Medical Affairs Scientific Manager, Benlysta, for reviewing our paper and making important contributions to improving it.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: RAL is a licensed professor of State University of Rio de Janeiro, currently working in GlaxoSmithKline (Upper Providence, PA, USA) as a Global Medical Expert. Other authors declare no conflict of interest regarding this paper.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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4.2 **Artigo 2 - Ocular involvement in primary antiphospholipid syndrome: results of an extensive ophthalmological evaluation performed in the APS-Rio cohort** (Artigo publicado)

Paper

Lupus
2022, Vol. 0(0) 1–9
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DOI: 10.1177/09612033221143294
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Ocular involvement in primary antiphospholipid syndrome: results of an extensive ophthalmological evaluation performed in the APS-Rio cohort

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Abstract

Objective: To study ophthalmological manifestations in a well-characterized primary antiphospholipid syndrome (PAPS) cohort (APS-Rio) and compare them with a healthy control group.

Methods: We examined PAPS patients and controls with an extensive ophthalmological evaluation, which included anamnesis, visual acuity, slit-lamp biomicroscopy, binocular indirect ophthalmoscopy, and retinography of the anterior and posterior segments of the eye. PAPS group also underwent angiography exam and optical coherence tomography using spectral domain technology (SD-OCT).

Results: 98 PAPS patients and 102 controls were included. The most common symptom in PAPS was amaurosis fugax (34.7% vs. 6.9%; $p = .001$). In the multivariate analyses, Raynaud's phenomenon was associated with amaurosis fugax (OR 3.71, CI:1.33–10.32; $p = .012$), and livedo correlated with hemianopia (OR 6.96, CI:1.11–43.72, $p = .038$) and diplopia (OR 3.49, CI:1.02–11.53, $p = .047$). After ophthalmological evaluation, 84 PAPS patients had ocular involvement (1.0% glaucoma, 94.0% posterior findings, 62.7% anterior findings, and 56.6% both posterior and anterior findings). Vascular tortuosity was more frequent in the PAPS group (63.2% vs. 42.2%; $p = .002$), as well as peripheral tortuosity (29.6% vs. 7.8%; $p < .001$). After excluding patients with atherosclerotic risk factors, peripheral vascular tortuosity was still statistically associated with PAPS (35.0 vs. 7.8%, $p < .001$). Triple positivity was more frequent in PAPS patients with peripheral vascular tortuosity than in those without this ocular finding (34.5% vs. 15.9%, $p = .041$).

Conclusion: Vasomotor phenomena are importantly related to ocular symptoms in PAPS. Vascular tortuosity was a frequent finding in PAPS patients. Peripheral vascular tortuosity was associated with triple positivity and might be a biomarker of ischemic microvascular retinopathy due to PAPS.

Keywords

Antiphospholipid syndrome, antiphospholipid antibodies, thrombosis, ophthalmology, eye, retina, vision, vascular tortuosity

Date received: 22 June 2022; accepted: 16 November 2022

Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by thrombosis and/or obstetrical morbidity that occurs in patients with persistent positivity for antiphospholipid antibodies (aPL).[1,2] These aPL include lupus anticoagulant (LA), and the isotypes IgM and IgG of both anticardiolipin (aCL) and anti-β2glycoprotein I (aβ2GPI). Deep vein thrombosis of the lower limbs is the most frequent manifestation of APS, while stroke is the

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most common arterial thrombotic manifestation.[1–3] Several APS-related manifestations beyond thrombotic and obstetric events, named as non-criteria manifestations, are very common and include thrombocytopenia, livedo reticularis, skin ulcers, valvopathy, some ocular changes, and many others.[2,3]

We have recently performed a systematic review of the literature[4] and found that up to 88% of PAPS patients present with both thrombotic and non-thrombotic ocular findings, including anterior and posterior segments, orbital and neuro-ophthalmological changes. However, we identified that studies systematically evaluating PAPS patients with comprehensive ophthalmology diagnostic tools are still lacking.

Better understanding of the ocular manifestations of APS is of great importance since blindness and retinal vaso-occlusive disease may account for damage accrual in these patients and may greatly impact quality of life.[5]

Therefore, the aim of the present study was to perform an extensive ophthalmological evaluation in a well-defined cohort of PAPS patients, irrespective of ocular complaints, in order to better characterize ocular manifestations in APS and to compare them with healthy controls.

Material and methods

Design of the study

A cross-sectional study was conducted in our PAPS cohort named APS-Rio between May 2018 and February 2020. A convenience sample of PAPS patients was selected, and all consecutive patients were classified according to current criteria of Sydney.[2] The control group was balanced according to age and sex in a proportion of 1:1. Both groups signed a consent form. All procedures followed the principles embodied in the Declaration of Helsinki and were in accordance with local statutory requirements. The project was submitted to the local ethics committee (Comissão de Ética em Pesquisa—Universidade do Estado do Rio de Janeiro) and was approved with the following registration number: CAAE 76694617100005259.

Criteria of inclusion and exclusion

Participants of both groups included were equal or above 18 years old. Exclusion criteria for both groups were history of dye allergy or serious cognitive impairment that could jeopardize the examination. In the PAPS group, patients with other rheumatic autoimmune diseases or other diseases (such as sickle cell disease) that could interfere with the interpretation of ocular findings were excluded. Still, we excluded PAPS patients without peripheral venous access to perform the fluorescein angiography study. In the control group, we selected the healthiest participants as possible. Therefore, we excluded from the control group those with atherosclerotic risk factors, namely, arterial hypertension, diabetes, dyslipidemia (defined as hypercholesterolemia), and smoking (ever). Definitions of atherosclerotic risk factors are described elsewhere.[6–8] We also excluded, in this group, women who had taken estrogen contraception within 6 months prior to the study.

Data collection

Demographical data were collected from interviews before ophthalmological examination and from electronic medical records. Besides, in the PAPS group, we attained to thrombotic and obstetrical criteria, criteria aPL, atherosclerosis risk factors, and non-criteria manifestations (valvopathy, nephropathy, thrombocytopenia, livedo reticularis, Raynaud's phenomenon, and migraine). Laboratory criteria aPL included 2 or more positive aPL assays at least 12 weeks apart, including: LA, detected according to the guidelines of the International Society on Thrombosis and Haemostasis ISTH)[9]; IgG and/or IgM aCL in serum or plasma, present in medium or high titer (>40 GPL or MPL, measured by standardized ELISA; Quanta Lite, Inova); and IgG and/or IgM aβ2GPI (>99th percentile, measured by standardized ELISA; Euroimmun, Inova).[2]

Ophthalmological evaluation

PAPS and control group underwent an extensive ophthalmological evaluation. This included an anamnesis regarding eye symptoms (visual deficit, amaurosis fugax, hemianopia, diplopia, headache with scotomas—definitions of symptoms are described elsewhere),[10–13] inflammatory symptoms, previous ocular disease, and previous eye surgery. Ophthalmological examination included the best-corrected visual acuity using Snellen test, intraocular pressure measurement with Goldmann applanation tonometry, slit-lamp biomicroscopy, binocular indirect ophthalmoscopy, and retinography of the anterior eye segment and all retina quadrants (Topcon TRC 50DX, Japan).

We additionally carried out fluorescein angiography (Topcon TRC 50DX, Japan) in PAPS patients, in order to search for ischemic areas. For ethical reasons, we could not justify an invasive procedure (angiography) in healthy controls. At the end, optical coherence tomography using spectral domain technology (SD-OCT) was performed to evaluate the macular area of PAPS patients (Spectralis OCT, Heidelberg Engineering, Germany).

Retinography documentation from anterior and posterior segment of all participants (PAPS and controls) was identified according to sex and age by decade for further analysis of 2 blinded ophthalmologists: telangiectasias and vascular tortuosity (AMMF and AMB) and maculopathy

(LSM and AMMF). Fluorescein angiography and SD-OCT were also analyzed by 2 ophthalmologists (AMMF, VC), but not in a blinded way, as only PAPS patients underwent these tests. Therefore, comparison of macular patterns between the two groups did not include angiography nor SD-OCT.

Regarding retinopathy, we specifically searched for drusen, hyper fluorescence caused by window defects, pigmentary changes, detachment of retinal pigment epithelium (DRPE), macular edema, epiretinal membrane, macular hole and lamellar hole, vitelliform dystrophy, retinal detachment, choroidal neovascularization, retinal and photoreceptors losses, intraretinal exudation, hemorrhages, and retinal ischemia, as appropriate for each method.

Statistical analysis

Statistical analysis was performed using SPSS version 22 program (Chicago, Illinois). Categorical variables were presented as numbers and were analyzed by Fisher's exact test or Pearson's chi-square. Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range and were analyzed by Student's t-test or Mann–Whitney U test, as appropriate. Normality was evaluated with graphical analysis and Kolmogorov–Smirnov test. Multivariate analysis was performed when feasible and was adjusted for age, sex, and variables with less than 0.10 in univariate analysis. A p-value less than 0.05 was considered statistically significant.

The agreement among ophthalmologists was performed using epiDisplay (Epidemiological Data Display Package, R package version 3.5.0.1).[14,15] According to kappa statistics, we correlated the strength of agreement (<0.00 poor; 0.00–0.20 slight; 0.21–0.40 fair; 0.41–0.60 moderate; 0.61–0.80 strong, and 0.81–1.00 almost perfect).[16,17] In all possible comparisons between groups and subgroups of examiners, for all outcomes, the hypothesis that the observed degrees of agreement were due to chance, at significance levels lower than 0.1%, was rejected.

Results

Initially, 138 PAPS patients were consecutively screened, and 98 were included. The main causes for exclusion were severe cognitive impairment after stroke (n = 2), history of dye allergy (n = 1), difficult peripheral venous access (n = 1), sickle cell disease (n = 1), Crohn's disease (n = 1), refusal to participate (n = 19), and lost to follow-up (n = 15). Then, 106 age and sex-matched controls were selected; however, 2 patients were excluded due to hypercholesterolemia, 1 was excluded due to diabetes, and 1 patient withdrew their consent. At the end, 98 patients (196 eyes) in the PAPS group and 102 participants (204 eyes) in the control group underwent ophthalmological examination. Flowchart of patient inclusion and exclusion is presented in Figure 1.

Both groups were comparable with no significant difference regarding median age (p = .075), female gender (p = .063), and ethnicity (p = .091). In the PAPS group, hypertension was observed in 40 patients (40.8%), diabetes mellitus in 9 patients (9.2%), dyslipidemia in 32 (32.7%), and smoking in 23 (23.5%). Considering criteria manifestations, thrombosis was present in 93.9% of patients. Arterial thrombosis was present in 37 patients (37.8%), meanwhile, venous thrombosis was present in 72 patients (73.5%). Only 6 patients (6.1%) had obstetrical criteria exclusively. Livedo was the leading non-criteria manifestation and was found in 23 (23.5%) of PAPS patients. Serological profile analysis showed 49 patients with single positivity to aPL (50.0%)—most of them LA isolated (47 patients—95.6% of them); 28 patients with double positivity (28.6%) and 21 patients (21.4%) with triple positivity. Eleven (11.2%) patients have used corticosteroids previously mainly for treatment of hematologic APS manifestations and 15 (15.3%) PAPS patients of our cohort were in use of hydroxychloroquine as an add-on thrombotic therapy. The characteristics of PAPS and control groups are summarized in Table 1.

PAPS patients had more eye symptoms than controls, all of them with statistically significant differences, except for migraine with aura (12.2% vs. 7.8%, p = .300). The most common symptom was amaurosis fugax (34.7% vs. 6.9%; p = .001), followed by diplopia (13.3% vs. 1.0%; p = .001) and hemianopia (10.2% vs. 1.0%; p = .004). Livedo was statistically correlated with a wide variety of ocular manifestations in the univariate analysis of PAPS patients: amaurosis fugax (p = .044), hemianopia (p<.001), and diplopia (p = .038). However, it remained associated only with hemianopia (OR 6.96, CI: 1.11–43.72, p = .038) and diplopia (OR 3.49, CI: 1.02–11.53, p = .047) in the multivariate analysis. Raynaud's phenomenon was related only to amaurosis fugax in both univariate (p = .007) and multivariate analysis (OR 3.71, CI: 1.33–10.32, p = .012). Patients with hypertension were more likely to present with amaurosis fugax and hemianopia in both univariate (p = .027 and p = .008, respectively) and multivariate analyses (OR 2.92, CI: 1.12–7.61, p = .029, and OR 26.72, CI: 1.33–536.19, p = .032, respectively). Finally, valvopathy correlated with amaurosis fugax (p = .012) and hemianopia (p < .001). Multivariate analysis confirmed the association between valvopathy and hemianopia (p = .042, OR 6.65, and CI: 1.07–11.53).

After ophthalmological evaluation, we detected 84 (85.7%) PAPS patients with ocular involvement. Of them, one (1.0%) patient had glaucoma, 78 (94.0%) had posterior findings, 52 (62.7%) had anterior findings, and 47 (56.6%) presented with both anterior and posterior involvement. We could not observe any differences for glaucoma (1.0% vs.

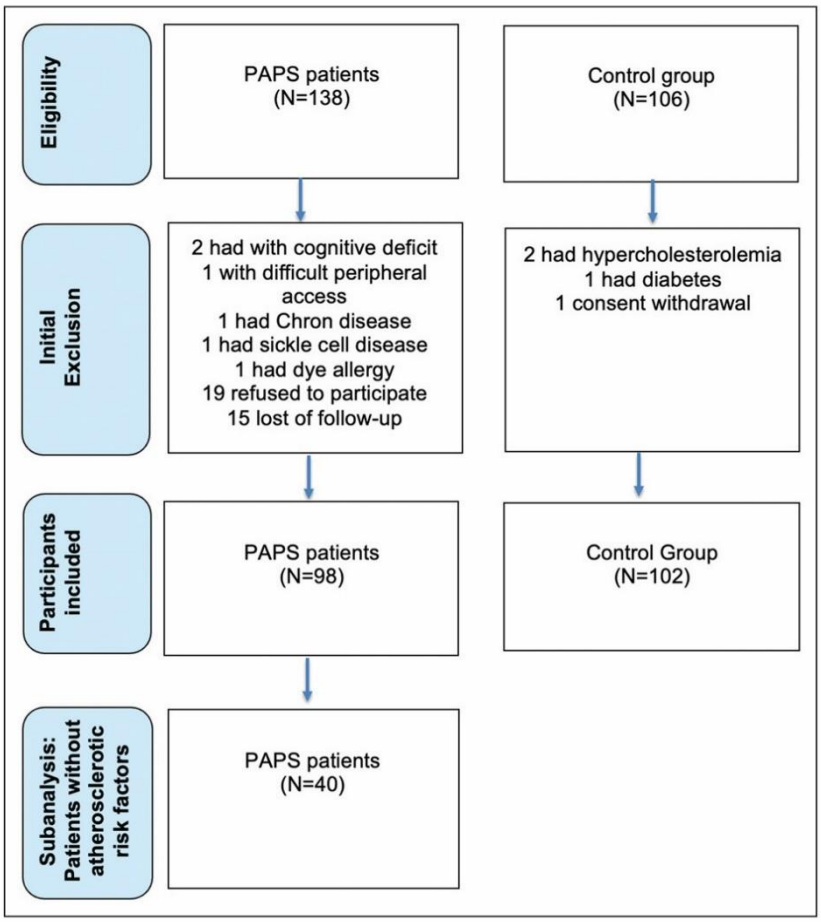

Figure 1. Flowchart of patient inclusion and exclusion.

0.0%, $p = .490$) between PAPS and controls, neither in the anterior segment—cataract (22.4% vs. 18.6%; $p = .503$), telangiectasias (40.8% vs. 33.3%; $p = .273$), and episcleritis (1.0% vs. 0.0%, $p = .490$). On the other hand, the posterior segment evaluated with retinography showed that vascular tortuosity was more common in the PAPS group than in controls (63.3% vs. 42.1%; $p = .002$), as well as peripheral tortuosity (29.6% vs. 7.8; $p < .001$) and maculopathy (37.8% vs. 16.7%; $p = .001$). The search for specific alterations in macula did not reveal any differences between groups, but drusen that were more common in PAPS patients (23.5% vs. 12.7%; $p = .048$). The ophthalmological symptoms and findings of both groups are summarized in Table 2.

Subsequently, we performed a subanalysis excluding PAPS patients who had atherosclerotic risk factors (hypertension, diabetes mellitus, dyslipidemia, and smoking) and compared the remaining PAPS patients to controls in order to verify if these retinal findings could be attributed to these comorbidities or to PAPS itself. Forty patients remained after this exclusion in the PAPS group. The previous findings of peripheral vascular tortuosity remained with significant statistical difference when compared to the control group (35.0% vs. 7.8%, $p < .001$). The same was not observed with maculopathy (27.5% vs. 20.6%, $p = .221$) or drusen (12.5% vs. 12.7; $p = .969$) (Table 3). Of note, 6 (16.2%) out of 37 PAPS patients with maculopathy evaluated by retinography were in use of hydroxychloroquine compared to 9 (14.8%) out of 61 PAPS patients without maculopathy ($p = .845$).

When we searched for alterations in angiography, we had 31 patients with posterior pole and/or peripheral hyperfluorescence caused by window defects, 19 with posterior pole and/or peripheral pigmentary changes, two peripheral areas of capillary non-perfusion, one with dark choroid, and one with retinal detachment. In SD-OCT, we also had four patients with macular edema, six with epiretinal membrane, nine with DRPE, two with

Table 1. Characteristics of primary antiphospholipid patients and controls.

Variable	PAPS (*N* = 98)	Controls (*N* = 102)	*p* value
Demographic characteristics			
Age (median, interquartile range)	44.5 (36.7–52.3)	42 (33.0–50.3)	0.075
Female gender, *n* (%)	88 (89.8)	82 (80.4)	0.063
Caucasian, *n* (%)	54 (55.1)	44 (43.1)	0.091
Atherosclerosis risk factors			
Hypertension, *n* (%)	40 (40.8)	—	—
Diabetes mellitus, *n* (%)	9 (9.2)	—	—
Dyslipidemia, *n* (%)	32 (32.7)	—	—
Smoking (ever), *n* (%)	23 (23.5)	—	—
Criteria manifestations			
Arterial thrombosis, *n* (%)	37 (37.8)	—	—
Venous thrombosis, *n* (%)	72 (73.5)	—	—
Obstetric, *n* (%)[a]	30 (30.6)	—	—
Non-criteria manifestations			
Valvulopathy, *n* (%)	8 (8.2)	—	—
Nephropathy, *n* (%)	2 (2.0)	—	—
Thrombocytopenia, *n* (%)	6 (6.1)	—	—
Livedo reticularis, *n* (%)	23 (23.5)	—	—
Serological profile			
Single positivity, *n* (%)	49 (50.0)	—	—
Double positivity, *n* (%)	28 (28.6)	—	—
Triple positivity, *n* (%)	21 (21.4)	—	—

PAPS = primary antiphospholipid syndrome.
[a]Excluded nulliparous women and male sex (*N* = 73).

Table 2. Ophthalmological symptoms and findings at examination in primary antiphospholipid syndrome and the control group.

Variable	PAPS (*N* = 98)	Controls (*N* = 102)	*p* value
Ophthalmological symptoms			
Amaurosis fugax, *n* (%)	34 (34.7)	7 (6.9)	0.001
Hemianopia, *n* (%)	10 (9.8)	1 (1.0)	0.004
Amaurosis, *n* (%)	3 (3.1)	1 (1.0)	0.293
Headache with scotomas, *n* (%)	8 (8.2)	12 (11.8)	0.300
Diplopia, *n* (%)	13 (13.3)	1 (1.0)	0.001
Ophthalmological findings			
Glaucoma, *n* (%)	1 (1.0)	0 (0)	0.490
Cataract, *n* (%)	12 (12.2)	19 (18.6)	0.503
Episcleritis, *n* (%)	1 (1.0)	0 (0)	0.490
Telangiectasias, *n* (%)	40 (40.8)	34 (33.3)	0.273
Vascular tortuosity, *n* (%)	63 (64.2)	43 (43.9)	0.002
Diffuse vascular tortuosity, *n* (%)	33 (33.7)	35 (34.3)	0.924
Peripheral vascular tortuosity, *n* (%)	29 (29.6)	8 (7.8)	<0.001
Maculopathy, *n* (%)	37 (37.8)	17 (16.7)	0.001
Maculopathy—Drusen, *n* (%)	23 (23.5)	13 (12.7)	0.048

PAPS = primary antiphospholipid syndrome.

vitelliform dystrophy, and eight with changes or losses in retinal layers. In summary, six cases had documented retinal vascular occlusive disease (6.1%) with three patients with retinal thrombosis and one with carotid thrombosis. Moreover, two patients showed no perfusion areas with absent neovascularization with one of them asymptomatic. Maculopathy was also not more prevalent in hydroxychloroquine users when PAPS patients were

examined by angiography (17.1% vs. 14.3%; $p = .707$) or by SD-OCT (17.1% vs. 14.0%; $p = .680$).

Neither thrombotic manifestations nor aPL profile were correlated to ocular findings at examination (data not shown), except for triple positivity with peripheral vascular tortuosity. The frequency of triple positivity in PAPS patients with peripheral vascular tortuosity was 34.5%, in contrast to 15.9% in PAPS patients without this ocular finding ($p = .041$). After the subanalysis excluding PAPS patients with atherosclerotic risk factors, this association was even more relevant, with 50% of triple positivity in patients with peripheral tortuosity against 15.4% in those without this vascular pattern ($p = .019$).

One patient had a rare ocular manifestation that is noteworthy. She was a 45-year-old woman with low vision for many years and positivity to LA. The anterior segment examination by slit lamp showed pellucid marginal corneal degeneration[18] in the left eye, a rare, non-inflammatory ectatic corneal disease with unclear etiology, and no opacified lens. It was confirmed by an additional exam of anterior segment tomography (Pentacam, Oculus, Germany). Electroretinography (ERG) was performed and showed injury in photoreceptors, with a Stargardt-like pattern, the most common recessively inherited macular dystrophy.[19]

The strength of agreement among ophthalmologists varied from strong to almost perfect. These findings are summarized in Table 4.

Discussion

Our study is the first to conduct an extensive ophthalmological evaluation in a well-characterized PAPS population compared with a control group.

The rates of different ocular complaints, such as amaurosis fugax, hemianopia, and diplopia, were statistically higher in PAPS patients, compared to controls. Among these symptoms, amaurosis fugax was the most commonly described. We found an association between amaurosis fugax and livedo in the univariate analysis, and between Raynaud's phenomenon in both univariate and multivariate analyses. These findings are similar to those reported in our previous retrospective study with 105 PAPS patients, but without comparison to a control group. We may speculate

Table 3. Ophthalmological findings (retinography) in primary antiphospholipid syndrome after excluding atherosclerotic risk factors compared to a healthy control group.

Ophthalmological findings	PAPS ($N = 40$)	Controls ($N = 102$)	p value
Telangiectasias, n (%)	10 (25.0)	34 (33.3)	0.334
Vascular tortuosity, n (%)	23 (57.5)	43 (43.9)	0.099
Diffuse vascular tortuosity, n (%)	9 (22.5)	35 (34.3)	0.171
Peripheral vascular tortuosity, n (%)	14 (35.0)	8 (7.8)	<0.001
Maculopathy, n (%)	10 (25.0)	17 (16.7)	0.255
Maculopathy—Drusen, n (%)	5 (12.5)	13 (12.7)	0.969

PAPS = primary antiphospholipid syndrome.

Table 4. Agreement among ophthalmologists, measures, coefficients, and kappa test.

			Kappa coefficient		
Ophthalmological findings	Ophthalmologist group	Agreement observed (%)	Statistic	Degree of agreement	Kappa test p value
Retinography					
Maculopathy	1, 2	96.94	0.9	Almost perfect	<0.001
Telangiectasia	1, 2	86.27	0.7	Strong	<0.001
Vascular tortuosity	1, 2	86.27	0.7	Strong	<0.001
Diffuse VT	1, 2	93.14	0.8	Almost perfect	<0.001
Peripheral VT	1, 2	91.67	0.7	Strong	<0.001
Angiography					
Maculopathy	1, 3	96.94	0.9	Almost perfect	<0.001
Stroma	1, 3	95.92	0.9	Almost perfect	<0.001
Choroid	1, 3	100	1.0	Almost perfect	<0.001
SD-OCT					
Maculopathy	1, 3	90.92	0.8	Strong	<0.001

SD-OCT = spectral domain optical coherence tomography. VT = vascular tortuosity *Ophthalmologist group: 1 = AMMF; 2 = LSM; and 3 = VC.

that a vasomotor response could explain the link between these cutaneous non-criteria manifestations of PAPS and amaurosis fugax.[4] Livedo also remained statistically associated with hemianopia and diplopia in the multivariate analysis. These symptoms may be representative of a past event of ischemic cerebral injury, and the association between livedo and stroke is well-described.[20] Furthermore, arterial hypertension, a strong risk factor for transient ischemic attack and stroke, was related to both amaurosis fugax and diplopia. In our study, valvopathy was associated with hemianopia. Pardos-Gea et al. described the association of valvopathy and stroke.[21] Therefore, ischemic cerebral manifestation may also be the explanation for this association.

Ocular involvement in APS patients is common and has been described as many as 88%.[22] These numbers may be overestimated because of lupus treatment. Menet et al. showed that most of the ocular manifestations in APS were iatrogenic related to corticosteroids or hydroxychloroquine.[23] Only a minority of our patients have been treated with these medications. Paradoxically, we found high rates of ocular manifestations (85.7%) in our study, which included only the primary form of the disease. The meticulous ocular examination of our PAPS patients might be the reason for these elevated numbers.

Regarding anterior segment findings, even though we had 40 telangiectasias in PAPS patients, there were no statistically significant differences between groups. Previous cross-sectional studies showed that the anterior segment is less affected when compared with posterior involvement, which is similar to our results.[24,25] In contrast, Miserocchi et al.[26] described a high number of anterior findings in ten out of 13 PAPS patients, but all these patients had ocular inflammation at presentation.

The posterior segment of the eye was the most common ocular involvement in our study, with particular attention to venous tortuosity, mainly peripheral tortuosity. Venous tortuosity has already been described as the most common posterior finding in PAPS.[24,25] Castañon et al. conducted a cross-sectional study with 17 patients and 13 of them were submitted to angiography. Venous tortuosity was found in 6 patients (46.1%).[24] Demirci et al. evaluated 22 PAPS patients and 18 of them performed ocular angiography and this ocular alteration was found in 45.5% of them.[25] However, this ophthalmological manifestation should be interpreted with caution, as venous tortuosity may be found in other diseases, such as hypertensive retinopathy.[24] Our healthy control group did not have any confounding risk factors for these findings. Therefore, in order to understand if these findings could be attributed to PAPS itself, we conducted a posterior analysis excluding PAPS patients with risk factors for atherosclerosis. Our results showed that the increased rates of venous tortuosity with peripheral involvement remained statistically significant compared to controls, even after adjusting for those confounding factors. The increased vessel tortuosity is an early sign for some hypoxia-implicated retinopathies[27] and may represent an ischemic finding affecting the microvasculature in APS. Interestingly, triple positivity, a marker of thrombotic prognosis in APS,[28] was also related to peripheral venous tortuosity. Vascular tortuosity is linked to early microvascular damage in diabetes,[29] and it is a prognostic factor in some other scenarios, like Fabry disease, indicating a more severe phenotype of disease.[30] We then hypothesize that this ocular alteration may represent an angiography biomarker of prognosis in PAPS.

Maculopathy was initially a significant finding in PAPS patients. However, this difference compared to controls disappeared when we excluded those PAPS patients with atherosclerotic risk factors. Macular findings related to APS in the literature are rare and mostly limited to isolated case reports. Choroidal neovascular membrane,[31] central serous chorioretinopathy,[32,33] and paracentral acute middle maculopathy[34] were previously described. Hydroxychloroquine, an add-on therapy in APS[35] had no effect in maculopathy in our cohort.

Among our relevant findings in fluorescein angiography, six cases had documented retinal vascular occlusive disease. Two patients showed no perfusion areas with absent neovascularization with one of them asymptomatic. Furthermore, the ocular examination of one patient unmasked a pellucid marginal corneal degeneration, a rare, non-inflammatory, ectatic corneal disease of unclear etiology,[18] which had never been described in APS. The same patient showed an injury in photoreceptors in ERG, with a Stargardt-like pattern, an inherited macular dystrophy.[19] Both findings are incidental and probably not related to APS.

Even though there is no specific ocular finding related to APS besides thrombosis, its complications can be vision threatening in many cases. Ocular findings may be identified even in asymptomatic patients. Peripheral vascular tortuosity had been described in PAPS,[24,25,36,37] but not after excluding risk factors for atherosclerosis and after comparing it to a control group. This unspecific pattern of retinopathy involving the posterior segment and its association with triple positivity suggests it could represent an ischemic retinopathy, but its real meaning remains obscure.

Our study has limitations. Firstly, the cross-sectional design prevents us from drawing definite conclusions regarding the prognostic value of those findings. Secondly, we were not able to perform angiography and SD-OCT in controls. However, it also has strengths. Our cohort of PAPS patients is very well-characterized, with a long-term follow-up. Also, we performed a very extensive ophthalmological evaluation of all PAPS patients who met inclusion criteria, irrespective of ocular complaints. Additionally, we compared patients with a significant number of healthy controls

to characterize if our findings could be attributable to PAPS itself. Finally, we were able to perform a subgroup analysis including only PAPS patients without risk factors for atherosclerosis, which reinforces the validity of our data.

In conclusion, vasomotor phenomena are importantly related to ocular symptoms in PAPS. Nonetheless, there was no specific ocular finding besides thrombosis. Vascular tortuosity was a frequent finding in PAPS patients when compared to controls, even after adjusting for traditional cardiovascular risk factors. Peripheral vascular tortuosity was associated with triple positivity and might be a biomarker of ischemic microvascular retinopathy due to PAPS. A periodic ophthalmological evaluation of PAPS patients may be warranted to potentially prevent vision loss. Hence, prospective studies are of utmost importance to a better understanding of ocular involvement in APS.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Data availability

The data that support the findings of this study are available from the corresponding author (FS), upon reasonable request.

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CONCLUSÃO

As manifestações oftalmológicas relacionadas à SAFP, tanto de natureza trombótica quanto inflamatória, podem ter efeito devastador sobre a qualidade de vida dos pacientes portadores dessa entidade. Nosso estudo, realizado em uma coorte bem definida com pacientes portadores de SAFP pareados com um grupo controle saudável, encontramos um elevado número de manifestações (85,7%), além da relação das manifestações relacionadas a fenômenos vaso motores com sintomas oculares e da tortuosidade vascular periférica e sua correlação com a tripla positividade, dando novas contribuições para o entendimento da síndrome. Estudos prospectivos são necessários para confirmar a importância do exame oftalmológico seriado na prevenção do acometimento ocular, bem como o possível papel das tortuosidades vasculares como marcadores precoces de prognóstico em pacientes com SAFP.

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APÊNDICE A - Critérios classificatórios da SAF (Continua)

Critérios clínicos*	Comentários
1- Trombose vascular	Um ou mais episódios clínicos de trombose arterial, venosa ou de pequenos vasos, em qualquer órgão em qualquer tecido ou órgão. Trombose deve ser confirmada por critérios objetivos validados (ex. achados inequívocos de estudos de imagem ou histopatológico). Para confirmação histopatológica, trombose deve estar presente sem evidência significativa de inflamação da parede do vaso
Morbidade gestacional	(a)uma ou mais mortes inexplicadas de um feto morfologicamente normal na décima semana ou mais de gestação, com feto morfologicamente normal documentado por ultrassonografia ou exame direto do feto, OU (b) Um ou mais nascimentos prematuros em um neonato morfologicamente normal antes da 34a semana de gestação por motivo de: (i) eclâmpsia ou pré-eclâmpsia grave de acordo com definições padrões, OU (ii) achados reconhecidos de insuficiência placentária, OU (c) Três ou mais abortos espontâneos inexplicados consecutivos antes da 10a semana de gestação, com exclusão de anormalidades anatômicas e hormonais maternas e de causas cromossomiais maternas e paternas

Critérios laboratoriais	Comentários
1-Anticoagulante lúpico (LAC)	presente no plasma em 2 ou mais ocasiões com pelo menos 12 semanas de intervalo, detectado de acordo com os Guidelines da Sociedade Internacional de Trombose e Hemostasia
2-Anticorpos anticardiolipina (aCL)	isotipo IgG e/ou IgM sérico ou plasmático, presente em títulos médios ou altos (ex. >40 GPL ou MPL, ou > que o percentil 99), em 2 ou mais ocasiões, com pelo menos 12 semanas de intervalo, medidos por ELISA.
3- Anticorpo Anti-β 2 glycoproteina-I((aβ2GPTN-I) do isotipo IgG e/ou IgM sérico ou plasmático (em títulos > que o percentil 99)	presentes em 2 ou mais ocasiões com pelo menos 12 semanas de intervalo, medido por ELISA, de acordo com procedimentos recomendados.

Nota: ***** A classificação deve ser evitada se há um espaço menor que 12 semanas ou maior que 5 anos separam o aPL e a manifestação clínica.

Fonte: Adaptado de *International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS)* (9).

APÊNDICE B - Termo de Consentimento Livre e Esclarecido - Pacientes SAF

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Eu,_____, estou sendo convidado(a) como voluntário(a) a participar da pesquisa: Manifestações Oculares da Síndrome do Anticorpo Antifosfolipídio **(SAF)**.

Por favor, leia o termo com bastante atenção antes de assiná-lo. Qualquer dúvida, seja de entendimento ou de algum termo médico, fique à vontade para perguntar ao pesquisador e à equipe da pesquisa.

A síndrome do anticorpo antifosfolipídio (SAF) é uma doença que causa tromboses e problemas na gestação (gravidez). Ela é frequentemente associada a outras doenças reumatológicas, como lúpus eritematoso sistêmico, síndrome de Sjögren, entre outras. Apesar de ser reconhecida há alguns anos, ainda existem muitas dúvidas com relação ao seu diagnóstico e tratamento. O objetivo de nossa pesquisa é tentar identificar os fatores de risco que contribuem para essas complicações, avaliar o perfil dos pacientes com SAF no Brasil e tentar melhora a qualidade do tratamento da doença.

Por que você foi convidado? Você foi escolhido porque recebeu o diagnóstico de síndrome do anticorpo antifosfolipídio (SAF), está em investigação para SAF ou possui alguma doença autoimune que possa ter associação com SAF.

Quais os benefícios de participar? A sua participação nesse estudo ajuda aos médicos conhecer melhor a doença, permitindo identificar fatores de risco para tromboses e problemas na gestação e avaliar meios de prevenir essas complicações; melhorar o conhecimento sobre o perfil de pacientes com SAF no Brasil; e melhorar a qualidade do tratamento da doença. Além disso, é possível se ter acesso a determinados tipos de exames que não são disponíveis no SUS, devido ao alto custo.

Nome	Assinatura do Participante	Data

Nome	Assinatura do Pesquisador	Data
Nome	Assinatura de Testemunha	Data

Caso você não queira participar, o que acontece? A participação é voluntária. Você é livre para não participar, retirar seu consentimento ou sair do estudo a qualquer momento. Você não deixará de ser atendido, nem receberá um tratamento pior, caso não queira participar da pesquisa.

Você terá alguma despesa? Não. Os pacientes que possuam dificuldade financeira para comparecer às consultas serão encaminhados ao serviço social do HUPE para receber orientações quanto ao benefício do passe-livre para consultas e exames, conforme já é realizado de rotina em nosso ambulatório.

Você terá algum ganho ou compensação em dinheiro? Não.

O que será realizado nessa pesquisa? A pesquisa envolve a realização de consultas médicas, coleta de exames de sangue para confirmação do diagnóstico de SAF e para acompanhamento do tratamento, realização de exames de imagem, avaliação oftalmológica, entre outros, conforme indicação médica. Não será oferecido nenhum tipo de medicamento novo em fases de testes como protocolo da pesquisa. Caso você engravide, nenhum risco será oferecido à sua gestação, uma vez que os exames serão realizados de acordo com a evolução da sua gravidez durante o pré-natal.

Favor marcar abaixo os exames que você autoriza que sejam solicitados/utilizados para a pesquisa:

☐ Exames de sangue de rotina, TAP/INR

☐ Pesquisa de antifosfolípides (confirmação do diagnóstico)

☐ Exames de imagem, conforme indicação médica (radiografia, tomografias, ressonâncias...)

☐ Ecocardiograma transtorácico

☐ Avaliação oftalmológica

☐ Outros exames, conforme necessidade e indicação médica

Nome	Assinatura do Participante	Data
Nome	Assinatura do Pesquisador	Data
Nome	Assinatura de Testemunha	Data

Quais os riscos de participar? O risco de participar são mínimos, uma vez que estão relacionados à coleta de exames de sangue e realização de exames adicionais. A coleta de sangue pode causar dor no local da punção e hematomas (principalmente em pacientes que fazem uso de anticoagulantes). Radiografias e tomografias emitem radiação, o que não ocorre com a ressonância magnética. O uso de contraste pode causar reações alérgicas e alteração na função dos rins, geralmente transitória. Nenhum tratamento experimental será oferecido. Como todos esses exames serão realizados conforme a indicação de um médico durante o seu acompanhamento, a pesquisa não envolve nenhum risco adicional para você.

Você será identificado? Não. Os dados que coletarmos serão sigilosos. Os resultados de consultas médicas e exames serão arquivados no prontuário do HUPE, que é protegido pelo sigilo médico. Seu nome ou o material que indique a sua participação não será liberado sem a sua permissão. Além disso, seu nome ou qualquer característica que permitam que você seja identificado não serão divulgados em trabalhos que possam resultar dessa pesquisa.

Uma cópia deste consentimento informado será arquivada no serviço de Reumatologia do HUPE e a outra será fornecida a você.

Afirmo que fui informado(a) dos objetivos da pesquisa acima de maneira clara e detalhada esclareci minhas dúvidas. Sei que em qualquer momento poderei solicitar novas informações e mudar minha decisão se assim o desejar. Os Dr. Flávio Signorelli e Adriana Franco certificaram-me de que todos os dados desta pesquisa serão confidenciais. Em caso de dúvidas poderei contactar os pesquisadores Flávio Signorelli e Adriana Franco no telefone (21) 2868-8083, E-mail.: flasigno@hotmail.com, adrimmfranco@yahoo.com.br ou procurar o

Comitê de Ética em Pesquisa do Hospital Universitário Pedro Ernesto, sito à Av. 28 de Setembro, 77 térreo. Tels.: 2868-8253, E-mail.: cep-hupe@uerj.br

Declaro que concordo em participar desse estudo. Recebi uma cópia deste termo de consentimento livre e esclarecido e me foi dada a oportunidade de ler e esclarecer as minhas dúvidas.

Nome	Assinatura do Participante	Data
Nome	Assinatura do Pesquisador	Data
Nome	Assinatura de Testemunha	Data

APÊNDICE C - Termo de Consentimento Livre e Esclarecido - pacientes controle

Eu,_____, estou sendo convidado(a) como voluntário(a) a participar da pesquisa: Manifestações Oculares da Síndrome do Anticorpo Antifosfolipídio **(SAF)**.

Por favor, leia o termo com bastante atenção antes de assiná-lo. Qualquer dúvida, seja de entendimento ou de algum termo médico, fique à vontade para perguntar ao pesquisador e à equipe da pesquisa.

A síndrome do anticorpo antifosfolipídio (SAF) é uma doença que causa tromboses e problemas na gestação (gravidez). Ela é frequentemente associada a outras doenças reumatológicas, como lúpus eritematoso sistêmico, síndrome de Sjögren, entre outras. Apesar de ser reconhecida há alguns anos, ainda existem muitas dúvidas com relação ao seu diagnóstico e tratamento. O objetivo de nossa pesquisa é tentar identificar os fatores de risco que contribuem para essas complicações, avaliar o perfil dos pacientes com SAF no Brasil e tentar melhora a qualidade do tratamento da doença.

Por que você foi convidado? Você foi escolhido porque NÃO tem Síndrome de Anticorpo Antifosfolipídio e NÃO possui fatores de risco para doença trombótica. Seu exame será usado como referência de exame sem alterações a serem comparados com os das pessoas que possuem SAF. Você fará parte do chamado "grupo controle"

Quais os benefícios de participar? A sua participação nesse estudo ajuda aos médicos conhecer melhor a doença, permitindo identificar fatores de risco para tromboses e problemas na gestação e avaliar meios de prevenir essas complicações; melhorar o conhecimento sobre o perfil de pacientes com SAF no Brasil; e melhorar a qualidade do tratamento da doença. Em outras palavras, você estará ajudando as pessoas portadoras dessa doença.

Nome	Assinatura do Participante	Data

Nome	Assinatura do Pesquisador	Data

Nome	Assinatura de Testemunha	Data

Caso você não queira participar, o que acontece? A participação é voluntária. Você é livre para não participar, retirar seu consentimento ou sair do estudo a qualquer momento. Você não deixará de ser atendido, nem receberá um tratamento pior, caso não queira participar da pesquisa.

Você terá alguma despesa? Não. Os pacientes que possuam dificuldade financeira para comparecer às consultas serão encaminhados ao serviço social do HUPE para receber orientações quanto ao benefício do passe-livre para consultas e exames, conforme já é realizado de rotina em nosso ambulatório.

Você terá algum ganho ou compensação em dinheiro? Não.

O que será realizado nessa pesquisa? A pesquisa envolve a realização de consulta médica com avaliação da retina e da córnea.

Quais os riscos de participar? O risco de participar são mínimos. Você não participará se tiver história de alergia a corantes, porque serão colocados colírios com corantes para avaliação do seu olho.

Nenhum tratamento experimental será oferecido. Como todos esses exames serão realizados conforme a indicação de um médico durante o seu acompanhamento, a pesquisa não envolve nenhum risco adicional para você.

Você será identificado? Não. Os dados que coletarmos serão sigilosos. Os resultados de consultas médicas e exames serão arquivados no prontuário do HUPE, que é protegido pelo

sigilo médico. Seu nome ou o material que indique a sua participação não será liberado sem a sua permissão. Além disso, seu nome ou qualquer característica que permitam que você seja identificado não serão divulgados em trabalhos que possam resultar dessa pesquisa.

Uma cópia deste consentimento informado será arquivada no serviço de Reumatologia do HUPE e a outra será fornecida a você.

Afirmo que fui informado(a) dos objetivos da pesquisa acima de maneira clara e detalhada e esclareci minhas dúvidas. Sei que em qualquer momento poderei solicitar novas informações e mudar minha decisão se assim o desejar. Os Dr. Flávio Signorelli e Adriana Franco

certificaram-me de que todos os dados desta pesquisa serão confidenciais. Em caso de dúvidas poderei contactar os pesquisadores Flávio Signorellie Adriana Franco no telefone (21) 2868-8083, E-mail.: flasigno@hotmail.com, adrimmfranco@yahoo.com.br ou procurar o Comitê de Ética em Pesquisa do Hospital Universitário Pedro Ernesto, sito à Av. 28 de Setembro, 77, térreo. Tels.: 2868-8253, E-mail.: cep-hupe@uerj.br

Declaro que concordo em participar desse estudo. Recebi uma cópia deste termo de consentimento livre e esclarecido e me foi dada a oportunidade de ler e esclarecer as minhas dúvidas.

Nome	Assinatura do Participante	Data
Nome	Assinatura do Pesquisador	Data
Nome	Assinatura da Testemunha	Data

ANEXO A - Aprovação do Comitê de Ética

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: Análise do perfil clínico e sorológico, do risco de eventos trombóticos e gestacionais e do tratamento em pacientes com Síndrome do Anticorpo Antifosfolípidio (SAF)

Pesquisador: FLAVIO VICTOR SIGNORELLI
Área Temática:
Versão: 3
CAAE: 76694617.1.0000.5259
Instituição Proponente: Faculdade de Ciências Médicas
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.106.379

Apresentação do Projeto:
Emenda para aprovação de documentação e alteração de informações relativas ao protocolo.

Objetivo da Pesquisa:
Emenda para aprovação de documentação e alteração de informações relativas ao protocolo.

Avaliação dos Riscos e Benefícios:
Emenda para aprovação de documentação e alteração de informações relativas ao protocolo.

Comentários e Considerações sobre a Pesquisa:
Justificativa da Emenda:
Houve necessidade da mudança do desenho experimental para um estudo de caso-controle, uma vez que se fez necessário saber se as alterações encontradas nos pacientes portadores de síndrome do annticorpo antifosfolipídeo teriam maior prevalencia do que na população saudável.

Continuação do Parecer: 4.106.379

Considerações sobre os Termos de apresentação obrigatória:

Os documentos enviados a este Comitê estão dentro das boas práticas em pesquisa e apresentando todos dados necessários para apreciação ética.

Conclusões ou Pendências e Lista de Inadequações:

A emenda apresenta todas as informações necessárias para avaliação ética. Diante do exposto e à luz da Resolução CNS nº466/2012, a Emenda pode ser enquadrada na categoria – APROVADO

Considerações Finais a critério do CEP:

Em consonância com a resolução CNS 466/12 e a Norma Operacional CNS 001/13, o CEP recomenda ao Pesquisador: Comunicar toda e qualquer alteração do projeto e no termo de consentimento livre e esclarecido, para análise das mudanças; Informar imediatamente qualquer evento adverso ocorrido durante o desenvolvimento da pesquisa; O Comitê de Ética solicita a V. Sª., que encaminhe relatórios parciais de andamento a cada 06 (seis) Meses da pesquisa e ao término, encaminhe a esta comissão um sumário dos resultados do projeto; Os dados individuais de todas as etapas da pesquisa devem ser mantidos em local seguro por 5 anos para possível auditoria dos órgãos competentes. **Este parecer foi elaborado baseado nos documentos abaixo relacionados:**

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1339613_E1.pdf	11/06/2020 10:14:21		Aceito
TCLE / Termos de Assentimento/ Justificativa de Ausência	TERMO_DE_CONSENTIMENTO_GRUPO_CONTROLE.docx	17/11/2019 20:31:46	FLAVIO VITOR SIGNORELLI	Aceito

Projeto Detalhado / Brochura Investigador	Projeto.docx	31/10/2017 21:46:22	FLAVIO VICTOR SIGNORELLI	Aceito
Outros	Resposta_pendencias.docx	31/10/2017 21:26:28	FLAVIO VICTOR SIGNORELLI	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.docx	31/10/2017 21:19:22	FLAVIO VICTOR SIGNORELLI	Aceito
Declaração de Pesquisadores	Vínculo_de_pesquisador.pdf	04/09/2017 19:05:10	FLAVIO VICTOR SIGNORELLI	Aceito
Folha de Rosto	Folha_de_rosto.pdf	04/09/2017 19:03:56	FLAVIO VICTOR SIGNORELLI	Aceito

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

RIO DE JANEIRO, 23 de junho de 2020.

_____

Assinado por:

WILLE OIGMAN

(Coordenador(a))

ANEXO B - Permissão para uso em tese do primeiro artigo científico

Mary Ann Price (she/her/hers) commented:

Dear Adriana M de M Franco,

Thank you for your request. You may include the Final Published PDF (or Original Submission or Accepted Manuscript) in your dissertation or thesis, which may be posted in an Institutional Repository or database as specified in our journal author reuse policy.**Please accept this email as permission for your request. Permission is granted for the life of the edition on a non-exclusive basis, in the English and Portuguese languages, throughout the world in all formats provided full citation is made to the original SAGE publication with a link to the appropriate DOI where possible. Permission does not include any third-party material found within the work.** Please contact us for any further use of the material and good luck on your dissertation!

Kind regards,

Mary Ann Price
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Mary Ann Price (she/her/hers) resolved this as Done.

How was our service for this request?

☆	☆	☆	☆	☆
Very poor	Poor	Neither good nor poor	God	Very good

ANEXO C - Permissão para uso em tese do segundo artigo científico

Craig Myles commented:
Dear Adriana M de M Franco,

Thank you for your ticket. As you are the author of "Ocular involvement in primary antiphospholipid syndrome: results of an extensive ophthalmological evaluation performed in the APS-Rio cohort," I am pleased to report we can grant your request to include your work without a fee as part of your thesis.
Please accept this email as permission for your request as detailed above. Permission is granted for the life of the thesis on a non-exclusive basis, in the English and Portuguese languages, throughout the world in all formats provided full citation is made to the original SAGE publication. Permission does not include any third-party material found within the work. Please contact us for any further usage of the material. If you have any questions, or if we may be of further assistance, please let us know.
Kind regards,
Craig Myles
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www.sagepublishing.com
Craig Myles resolved this as Done.
How was our service for this request?

☆	☆	☆	☆	☆
Very poor	Poor	Neither good nor poor	God	Very good