Associations between infections and Antiphospholipid Syndrome

Gilian Crowther MA (Oxon), FBANT, mNNA, mANP, CNHC reg.
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Agenda

- **Mechanisms by which infections can trigger antiphospholipid antibodies/syndrome**
- Viral involvement
- Bacterial involvement
- Infections indicated

Schoenfeld: Many infections are associated with increases in antiphospholipid antibodies (aPL)

Ann Rheum Dis. 2006 Jan;65(1):2–6. doi: 10.1136/ard.2005.045443

Infectious origin of the antiphospholipid syndrome*

Y Shoenfeld [1,2,3], M Blank [1,2,3], R Cervera [1,2,3], J Font [1,2,3], E Raschi [1,2,3], P-L Meroni [1,2,3]

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Short abstract

From a systemic disease towards the infectious aetiology

Keywords: anticardiolipin, antiphospholipid syndrome, autoantibodies, autoimmunity, infection

The general consensus is that autoimmune diseases have a multifactorial aetiology, depending on both genetic and environmental factors. Microbial agents or viruses can induce autoimmune diseases by a variety of mechanisms.[1] For example, proteins of certain infectious agents can act as polyclonal activators on unique lymphocyte subsets. Viruses can preferentially infect/destroy a particular T cell subset, leading to an imbalance in the immune response. Several microbial agents have been found to encode superantigens that can selectively activate subset(s) of T cells. Microbes can also direct the release of cytokines and chemokines, which can act as growth, differentiation, or chemotactic factors for different cell populations and regulate expression of major histocompatibility complex class I and class II as well as costimulatory molecules.[2]

Source: Shoenfeld Y, Blank M, Cervera R, Font J, Raschi E, Meroni PL. Infectious origin of the antiphospholipid syndrome. Ann Rheum Dis. 2006 Jan;65(1):2-6.

"Pathogenic aPL may be generated in APS by a molecular mimicry mechanism"

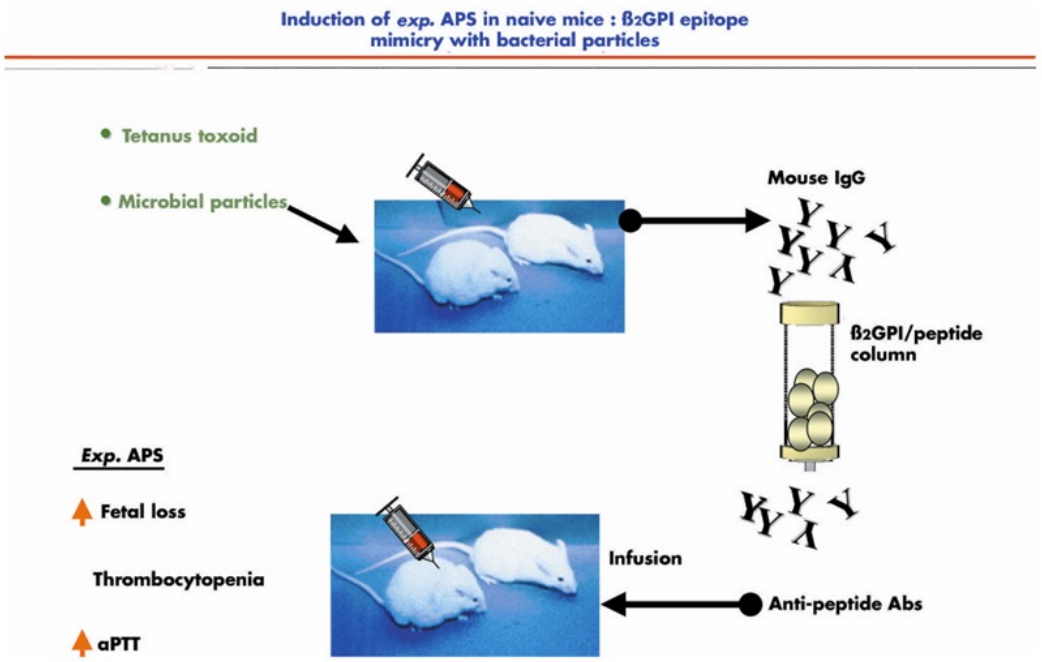

Figure 2 Active immunisation of mice with bacterial and viral particles induces anti- β_2GPI antibodies. The anti-β_2GPI antibodies when passively infused into another set of naive mice induce experimental APS.

enhanced thrombus formation in vivo. These results indicate that aPL induced by immunisation with a phospholipid-binding CMV peptide are pathogenic in vivo. The results also suggest a molecular mimicry mechanism by which pathogenic aPL may be generated in patients with APS.

"Pathogenic aPL may be generated in APS by a molecular mimicry mechanism"

Moreover, we assessed the ability of a β_2GPI related synthetic peptide (NTLKTPRVGGC),[31] which is similar to

of prevention and/or treatment of thrombosis in APS.[31]

Recently, our group pointed to the possibility that Libman-Sacks non-bacterial endocarditis occurring in patients with APS may have an infectious origin.[32] This proposal was based on a previous study in which aPL/β_2GPI antibodies were located on the deformed human valves derived from patients with APS.[33] The fine antigenic specificity of the deposited aPL was determined by (*a*) identifying their ability to bind biotinylated TLRVYK peptide and (*b*) by showing that the same peptide could inhibit the binding of S2.9 (a monoclonal antibody specific

particles, which share structural homology (molecular mimicry) with the β_2GPI molecule. Whether a person will develop APS will depend mainly on his genetic predisposition, which may or may not favour the production of the cross reacting autoantibodies.

β_2GPI polymorphism (in particular the Val^{247} allele) has recently been associated with both a high frequency of anti-β_2GPI antibodies and stronger antibody reactivity than the Leu^{247} β_2GPI allele.[34 35] Such a finding may represent an additional variable that might favour the occurrence of molecular mimicry between infectious molecules and molecular variants of the aPL

Source: Shoenfeld Y, Blank M, Cervera R, Font J, Raschi E, Meroni PL. Infectious origin of the antiphospholipid syndrome. Ann Rheum Dis. 2006 Jan;65(1):2-6.

“Undisputable coincidence” raises question as to whether infections associated with aPL may be pathogenic

antibodies MDPI

▸ Antibodies (Basel). 2016 Jun 2;5(2):15. doi: 10.3390/antib5020015

Antiphospholipid Antibodies: Their Origin and Development

Karl J Lackner [1,*], Nadine Müller-Calleja [1]

Editor: Ricard Cervera[1]

2.2. Infections and aPL

In humans, many infectious diseases are associated with a transient or permanent rise of aPL of the IgM and IgG isotype. These include viral infections, e.g., parvovirus B-19, cytomegalovirus (CMV) and hepatitis C, as well as bacterial and parasitic infections, e.g., syphilis or helicobacter pylori infection [26]. Even though the production of specific aPL by the adaptive immune system cannot be ruled out and molecular mimicry is proposed as one possible underlying mechanism [27–31], the high frequency of a uniform antibody response to extremely different antigens should alert to the possibility of induction of natural antibodies. Another interesting aspect of the association of viral infections with aPL is the fact that there is a significant number of patients who develop thrombotic events [26,32–34]. While it is not proven that these events are caused by aPL, the undisputable coincidence raises the question whether these infection associated aPL may be pathogenic.

Source: Lackner KJ, Müller-Calleja N. Antiphospholipid Antibodies: Their Origin and Development. Antibodies (Basel). 2016 Jun 2;5(2):15.

Agenda

- Mechanisms by which infections can trigger antiphospholipid antibodies/syndrome
- **Viral involvement**
- Bacterial involvement
- Infections indicated

Viral infections can increase the risk of developing elevated antiphospholipid antibodies

HIV, HBV, HCV, EBV, Parvo B19

Table 1 Viral infections associated with aPL and APS manifestations

Main infections	aCL isotype	Anti-β2GPI	APS manifestations OR (95% CI)	
			Thromboembolic events	Pregnancy events
Viral				
HIV	IgG	IgM	7.4 (0.24–231.3)	
HBV	IgM	–	3.1 (0.19–49.7)	
HCV	IgG, IgM	IgA	3.4 (1.6–7.4)	
Epstein-Barr virus	IgM	IgA, IgM	Non-estimable	
Parvovirus B19	IgG	+	–	1.7 (0.17–17.6)

Anti-β2GPI anti-β2 glycoprotein I, *aCL* anticardiolipin antibodies, *aPL* antiphospholipid antibodies, *CI* confidence interval, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *LA* lupus anticoagulant, *ND* not detected

"Several studies have shown there is an increased risk of developing aPL in various infections, particularly viral infections …. Clinicians should be aware of clinical features suggestive of APS in patients with viral infections."

Source: Mendoza-Pinto C et al. Role of Infectious Diseases in the Antiphospholipid Syndrome (Including Its Catastrophic Variant). Curr Rheumatol Rep. 2018 Aug 20;20(10):62

Case reports provide evidence for CMV being the causal factor inducing antiphospholipid antibody syndrome

CMV

Volume 24, Issue 2
February 1997

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JOURNAL ARTICLE

Antiphospholipid Syndrome Associated with Cytomegalovirus Infection: Case Report and Review

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Jaime A. Labarca ✉, Ricardo M. Rabaggliati, Francisco J. Radrigan, Paula P. Rojas, Carlos M. Perez, Marcela V. Ferrés, Guillermo G. Acuña, Pablo A. Bertin

Clinical Infectious Diseases, Volume 24, Issue 2, February 1997, Pages 197–200,
https://doi.org/10.1093/clinids/24.2.197
Published: 01 February 1997 **Article history** ▾

Abstract

Antiphospholipid antibodies are commonly related to connective tissue disorders, the use of certain drugs, and infection. It is thought that antiphospholipid syndrome (APS) is associated primarily with connective tissue disorders. We describe a healthy young male who had an episode of APS that was associated with cytomegalovirus infection and who developed mesenteric and femoropopliteal thrombosis. He responded well to treatment with anticoagulants; 6 months after the onset of APS, IgM and IgG anticardiolipin antibody titers declined. We point out the importance of screening for infectious agents in cases of APS; if the agents are identified, APS may be

2

"Recent case reports provide evidence for CMV being the causal factor inducing antiphospholipid antibody syndrome (APS) with associated vascular thrombosis."[1]

"We point out the importance of screening for infectious agents in cases of APS; if the agents are identified, APS may be transitory."[2]

Source: 1. Denham C, Tissier G, Golding A. Antiphospholipid antibody syndrome with thrombotic splenic infarcts associated with acute cytomegalovirus infection. Access Microbiol. 2019 Jun 10;1(7):e000032; 2. Labarca JA et al. Antiphospholipid syndrome associated with cytomegalovirus infection: case report and review. Clin Infect Dis. 1997 Feb;24(2):197-200.

Parvovirus B19 status of 40 adult IgG aPL-positive patients showed that 33 (83%) were anti-IgG VP1/VP2-positive

Parvo B19

Arthritis Rheum. 2003 Jul;48(7):1939-47. doi: 10.1002/art.11038.

Antiphospholipid antibodies in pediatric and adult patients with rheumatic disease are associated with parvovirus B19 infection

Philipp Von Landenberg [1], Hartwig W Lehmann, Antje Knöll, Simone Dorsch, Susanne Modrow

Affiliations + expand

PMID: 12847688 DOI: 10.1002/art.11038

Free article

Abstract

Objective: To show a possible association between parvovirus B19 infection and the presence of antiphospholipid antibodies (aPL) in patients with rheumatic diseases.

Methods: Serum samples obtained from 88 children with various forms of juvenile rheumatic disease and from 40 adults with systemic lupus erythematosus, the antiphospholipid syndrome, or other rheumatic disease, who had previously been tested and shown to be positive for IgG aPL, were analyzed for the presence of B19 DNA, for antibodies against the B19 viral proteins VP1, VP2, and NS1, and for IgG aPL (anticardiolipin, anti-beta(2)-glycoprotein I, and antiphosphatidylserine). As controls, serum samples obtained from 135 children with noninflammatory bone diseases or growth retardation were also analyzed.

Results: Twenty-four (27%) of the 88 children with rheumatic diseases had detectable amounts of IgG aPL. Fourteen (58%) of these 24 IgG aPL-positive patients showed IgG against VP1/VP2 and viral genomes, indicating the presence of acute (2 patients) or persistent (12 patients) infection. Past parvovirus B19 infection was identified in 7 (29%) of 24 IgG aPL-positive children, as indicated by VP1/VP2-specific IgG in the absence of viral DNA. Three (12%) of 24 IgG aPL-positive children had not been infected with B19. Sixty-nine (51%) of 135 control children displayed VP1/VP2-specific IgG. Three (2%) of these 135 children were IgG aPL positive (2 children had past parvovirus B19 infection, and 1 was negative for parvovirus B19). Analysis of the parvovirus B19 status of 40 adult IgG aPL-positive patients showed that 33 (83%) were anti-IgG VP1/VP2-positive, and viral DNA was detected in 11 patients (28%). Ten of these 11 viremic patients were in the subgroup of 28 IgG aPL-positive SLE patients.

Source: Von Landenberg P et al. Antiphospholipid antibodies in pediatric and adult patients with rheumatic disease are associated with parvovirus B19 infection. Arthritis Rheum. 2003 Jul;48(7):1939-47.

“SARS-CoV-2 infection may induce antiphospholipid syndrome characterized by sustained elevation in antiphospholipid antibody levels”[1]

SARS-CoV-2

Autoimmunity Reviews 21 (2022) 103206

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Autoimmunity Reviews

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COVID-19 and the antiphospholipid syndrome

Manuel Serrano [a], Gerard Espinosa [b], Antonio Serrano [a], Ricard Cervera [b,*]

[a] Department of Immunology, Healthcare Research Institute I+12, Hospital 12 de Octubre, Madrid, Spain
[b] Department of Autoimmune Diseases, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Catalonia, Spain

ARTICLE INFO

Keywords:
COVID-19
Antiphospholipid syndrome
Antiphospholipid antibodies
Coagulopathy
Thrombosis

ABSTRACT

Coronavirus disease 2019 (COVID-19) has resulted in a global pandemic. Most COVID-19 patients are asymptomatic or have flu-like symptoms. However, around 15% of the patients may have severe disease, including unilateral or bilateral pneumonia with acute respiratory distress syndrome and progressive hypoxemia that may require mechanical ventilation assistance. A systemic inflammatory response syndrome occurs in the most severe forms of COVID-19, with multiorgan involvement which can be life threatening caused by a cytokine storm. Although what best characterizes COVID-19 are the manifestations of the respiratory system, it has been shown that it also acts at the cardiovascular level, producing coagulation abnormalities, which causes thrombotic events mainly in the arteries/arterioles, microcirculation and venous system, and potentially increased mortality risk. This multiorgan vascular disease overlaps with other known microangiopathies, such as thrombotic microangiopathy or paroxysmal nocturnal hemoglobinuria, where complement overactivation plays an important role in the pathophysiology of thrombosis. Furthermore, coagulopathy secondary to COVID-19 occurs in the context of an uncontrolled inflammatory response, reminiscent of APS, especially in its catastrophic form. This review summarizes the current knowledge regarding the relationship between COVID-19 and the APS.

1. Introduction

Coronavirus disease 2019 (COVID-19), an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a global pandemic. Most COVID-19 patients are asymptomatic or have flu-like symptoms [1]. However, around 15% of the patients may have severe disease, including unilateral or bilateral pneumonia with acute respiratory distress syndrome (ARDS) and progressive hypoxemia that may require mechanical ventilation assistance. A systemic

question whether SARS-CoV2 can produce a loss of host tolerance, triggering an autoimmune disease [7]. The deregulation of the immune response has been shown to be a key element in the unefficient responses against viruses. It is well known that cytomegalovirus, parvovirus B19, and Epstein-Barr virus (EBV) are environmental triggers of autoimmunity in genetically predisposed individuals [8]. These viruses can trigger autoimmunity through various mechanisms, such as the tendency to cause persistent infection, modulate the host's immune response by causing loss of self-tolerance producing autoreactive lymphocytes, or

Source: 1. Ren ZF et al. The well-defined antiphospholipid syndrome induced by COVID-19: a rare case report and review of the literature. Thromb J. 2024 Nov 8;22(1):99; errano M, Espinosa G, Serrano A, Cervera R. COVID-19 and the antiphospholipid syndrome. Autoimmun Rev. 2022 Dec;21(12):103206

50% of Covid-19 patients are positive for lupus anticoagulant in some studies

SARS-CoV-2

Best Practice & Research Clinical Haematology 35 (2022) 101402

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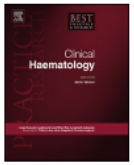

COVID-19 and antiphospholipid antibodies

Ayesha Butt [a], Doruk Erkan [b], Alfred Ian Lee [a,*]

[a] Section of Hematology, Department of Medicine, Yale School of Medicine, 333 Cedar St., New Haven, CT, 06520, USA
[b] Barbara Volcker Center for Women and Rheumatic Diseases, Hospital for Special Surgery and Weill Cornell Medicine, 535 E. 70th St., 6th floor, New York, NY, 10021, USA

ARTICLE INFO

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Lupus anticoagulant
Anticardiolipin antibodies
Beta-2 glycoprotein-1 antibodies
COVID-19 vaccination
Immunothrombosis

ABSTRACT

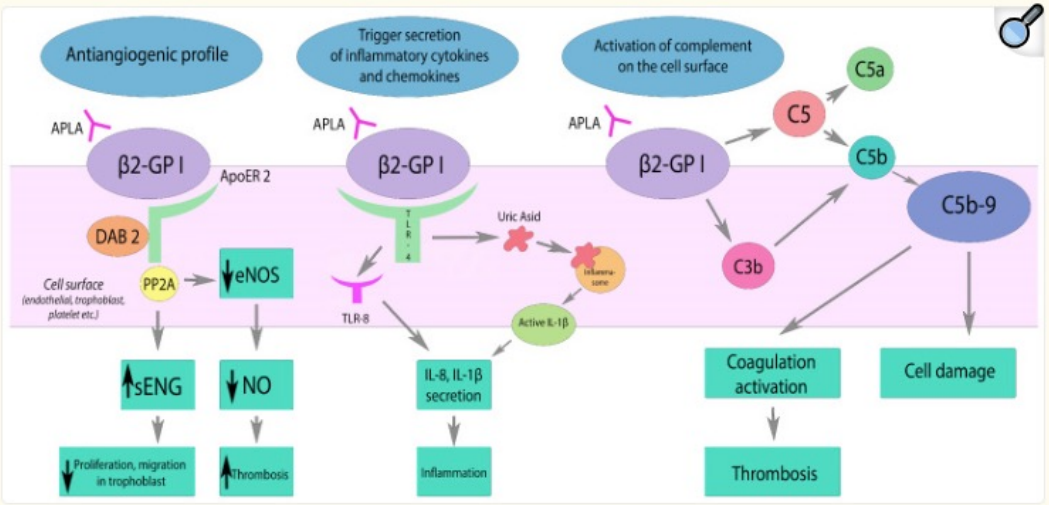
Antiphospholipid syndrome and the coagulopathy of COVID-19 share many pathophysiologic features, including endotheliopathy, hypercoagulability, and activation of platelets, complement pathways, and neutrophil extracellular traps, all acting in concert via a model of immunothrombosis. Antiphospholipid antibody production in COVID-19 is common, with 50% of COVID-19 patients being positive for lupus anticoagulant in some studies, and with non-Sapporo criteria antiphospholipid antibodies being prevalent as well. The biological significance of antiphospholipid antibodies in COVID-19 is uncertain, as such antibodies are usually transient, and studies examining clinical outcomes in COVID-19 patients with and without antiphospholipid antibodies have yielded conflicting results. In this review, we explore the biology of antiphospholipid antibodies in COVID-19 and other infections and discuss mechanisms of thrombogenesis in antiphospholipid syndrome and parallels with COVID-19 coagulopathy. In addition, we review the existing literature on safety of COVID-19 vaccination in patients with antiphospholipid antibodies and antiphospholipid syndrome.

"Antiphospholipid antibody production in COVID-19 is common, with 50% of COVID-19 patients being positive for lupus anticoagulant in some studies, and with non-Sapporo criteria antiphospholipid antibodies being prevalent as well."

Source: Butt A et al. COVID-19 and antiphospholipid antibodies. Best Pract Res Clin Haematol. 2022 Sep;35(3):101402.

Anti-β2GP1 is PRECISELY the antibody being found in severe COVID cases[1]

Figure 1.



Open in a new tab

Effects of APLA on the complement system, inflammation, and vascular tone. β2GP1—β2-glycoprotein I, ApoER2—apolipoprotein E2 receptor, DAB2—Disabled-2, PP2A—Protein phosphatase 2A, eNOS—nitric oxide synthase, sENG—soluble Endoglin, TLR-4—toll-like receptor 4, TLT-8—toll-like receptor 8. APLA reduces eNOS activity via ApoER2 interaction. Decreased NO production results in impaired vasodilatation and endothelial dysfunction. APLA activates TLR and inflammasome pathways, triggering the secretion of inflammatory cytokines and chemokines. APLA activates complement on the cell surface, leading to the coagulation activation and cell damage by C5b-9 deposition. Black arrow down—decrease; black arrow up —increase.

2

*APLA = antiphospho-lipid antibodies

APLA* affects many elements of the hemostatic system, and the main pathogenetic mechanisms can be divided into four groups:

(1)cellular activation (endothelial, immune cells, platelets),

(2)inhibition of anticoagulant potential,

(3)inhibition of fibrinolysis,

(4)activation of complement system

Figure 1 2

Source: 1. https://wmcresearch.substack.com/p/mellor-pita-et-al-july-3rd-p; ide ; 2. Bitsadze V et al. Catastrophic Antiphospholipid Syndrome. Int J Mol Sci. 2024 Jan 4;25(1):668

APLA become thrombogenic in the presence of an inflammatory stimulus

Anti-β2GP1 is PRECISELY the antibody being found in severe COVID cases[1, 2]

APLA = antiphospho-lipid antibodies

"APLA- β2GP1 complexes become thrombogenic in the presence of an inflammatory stimulus"[2]

WMC Research

Is CAPS an eventual common complication (fate?) from repeated infections/exposures to the Spike Protein?

WALTER M CHESNUT
JUL 16, 2024

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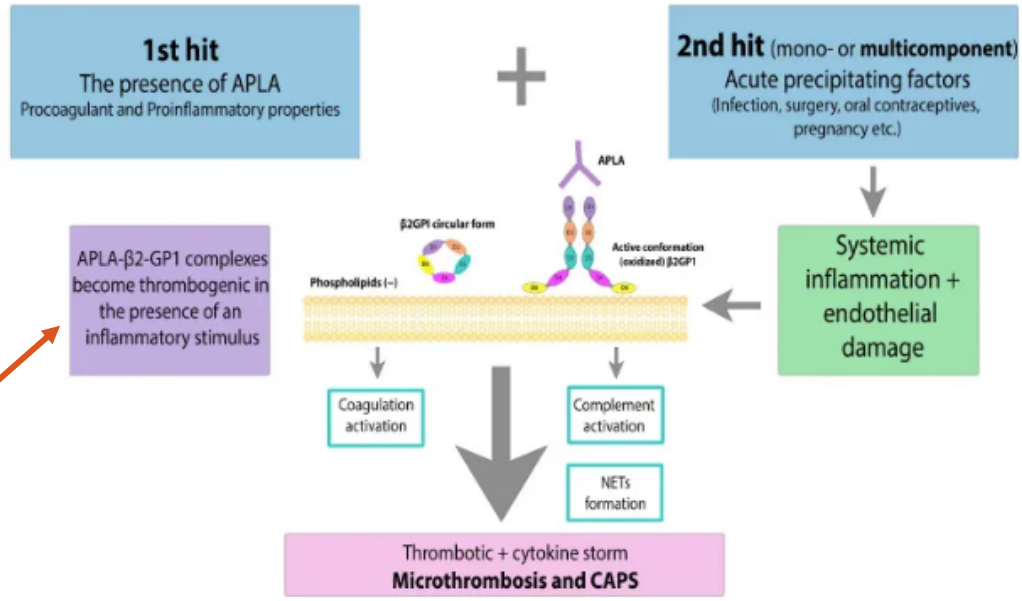
Covid the 2nd hit?



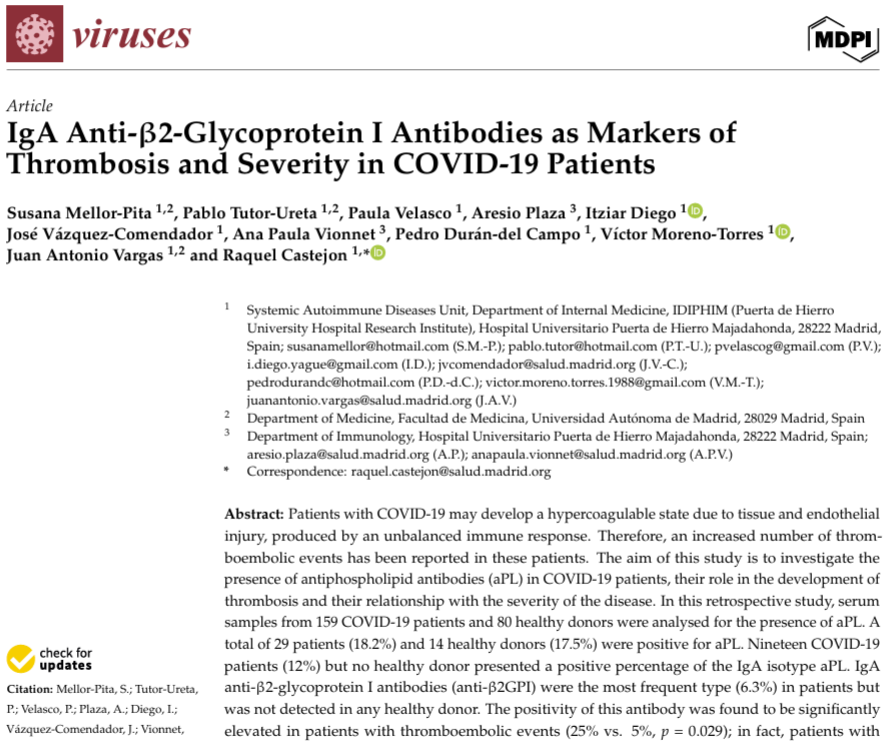
CAPS: the "two-hit" theory. APLA—antiphospholipid antibody, β2GPI—β2-glycoprotein I. Acute precipitating factors as a 2nd hit lead to systemic inflammation and endothelial damage. Massive cytokine release, NET formation and coagulation activation result in microthrombosis and CAPS.

1. https://wmcresearch.substack.com/p/mellor-pita-et-al-july-3rd-p; ide; 2 Bitsadze V et al. Catastrophic Antiphospholipid Syndrome. Int J Mol Sci. 2024 Jan 4;25(1):668

SARS-CoV-2 appears able to create a perfect storm

SARS-CoV-2

"Mellor-Pita et al., (July 3rd) Provide Convincing Evidence for my 2020 Hypothesis that the Spike Protein Induces Catastrophic Antiphospholipid Syndrome (CAPS)"[2]



viruses MDPI

Article

IgA Anti-β2-Glycoprotein I Antibodies as Markers of Thrombosis and Severity in COVID-19 Patients

Susana Mellor-Pita [1,2], Pablo Tutor-Ureta [1,2], Paula Velasco [1], Aresio Plaza [3], Itziar Diego [1], José Vázquez-Comendador [1], Ana Paula Vionnet [3], Pedro Durán-del Campo [1], Víctor Moreno-Torres [1], Juan Antonio Vargas [1,2] and Raquel Castejon [1,*]

[1] Systemic Autoimmune Diseases Unit, Department of Internal Medicine, IDIPHIM (Puerta de Hierro University Hospital Research Institute), Hospital Universitario Puerta de Hierro Majadahonda, 28222 Madrid, Spain; susanamellor@hotmail.com (S.M.-P.); pablo.tutor@hotmail.com (P.T.-U.); pvelascog@gmail.com (P.V.); i.diego.yague@gmail.com (I.D.); jvcomendador@salud.madrid.org (J.V.-C.); pedrodurandc@hotmail.com (P.D.-d.C.); victor.moreno.torres.1988@gmail.com (V.M.-T.); juanantonio.vargas@salud.madrid.org (J.A.V.)
[2] Department of Medicine, Facultad de Medicina, Universidad Autónoma de Madrid, 28029 Madrid, Spain
[3] Department of Immunology, Hospital Universitario Puerta de Hierro Majadahonda, 28222 Madrid, Spain; aresio.plaza@salud.madrid.org (A.P.); anapaula.vionnet@salud.madrid.org (A.P.V.)
* Correspondence: raquel.castejon@salud.madrid.org

Abstract: Patients with COVID-19 may develop a hypercoagulable state due to tissue and endothelial injury, produced by an unbalanced immune response. Therefore, an increased number of thromboembolic events has been reported in these patients. The aim of this study is to investigate the presence of antiphospholipid antibodies (aPL) in COVID-19 patients, their role in the development of thrombosis and their relationship with the severity of the disease. In this retrospective study, serum samples from 159 COVID-19 patients and 80 healthy donors were analysed for the presence of aPL. A total of 29 patients (18.2%) and 14 healthy donors (17.5%) were positive for aPL. Nineteen COVID-19 patients (12%) but no healthy donor presented a positive percentage of the IgA isotype aPL. IgA anti-β2-glycoprotein I antibodies (anti-β2GPI) were the most frequent type (6.3%) in patients but was not detected in any healthy donor. The positivity of this antibody was found to be significantly elevated in patients with thromboembolic events (25% vs. 5%, $p = 0.029$); in fact, patients with

Citation: Mellor-Pita, S.; Tutor-Ureta, P.; Velasco, P.; Plaza, A.; Diego, I.; Vázquez-Comendador, J.; Vionnet,

"My hypothesis is based on molecular mimicry, which is a CAPS development mechanism … What I observed in 2020 was that the molecular mimicry of the Spike Protein would cause systemic autoimmune disease. The most immediately devastating of which would be CAPS. As the evidence pours in, there is a significant amount that points to this. **I believe we need screening in the general population as well as those who are suffering from repeated infections to determine the presence and level of these antibodies and their trends over time.**" [2]

Source: Mellor-Pita S et al. IgA Anti-β2-Glycoprotein I Antibodies as Markers of Thrombosis and Severity in COVID-19 Patients. Viruses. 2024 Jul 3;16(7):1071. https://www.mdpi.com/1999-4915/16/7/1071; 2. https://wmcresearch.substack.com/p/mellor-pita-et-al-july-3rd-provide

Agenda

- Mechanism by which infections can trigger antiphospholipid antibodies/syndrome
- Viral involvement
- **Bacterial involvement**
- Infections indicated

A number of different bacteria have been associated with APS

Mycoplasma, Coxiella, parasitic, fungal

Table 2 Frequency of aPL antibodies and APS manifestations in patients with bacterial, parasitic and fungal infections

Main infections	Frequency of aPL positivity	Frequency of APS manifestations
Bacterial		
Coxiella burnetii	17.2%	3.9%
Mycoplasma pneumonia	2.2%	8.6%
Streptococci	2.2%	6.9%
Mycobacterium tuberculosis	2.2%	3.9%
Mycobacterium leprae	1.1%	4.2%
Parasitic	5.4%	4.2%
Fungal	2.2%	1.6%

From [22]

aPL antiphospholipid antibodies, *APS* antiphospholipid syndrome

Springer

Source: Mendoza-Pinto C et al. Role of Infectious Diseases in the Antiphospholipid Syndrome (Including Its Catastrophic Variant). Curr Rheumatol Rep. 2018 Aug 20;20(10):62.

Substantial number of patients with Mycoplasma pneu- induced respiratory disease have antiphospholipid antibodies

Myco

Antiphospholipid antibodies and Mycoplasma pneumoniae infection.

N Snowden [1], P B Wilson [1], M Longson [1], R S Pumphrey [1]

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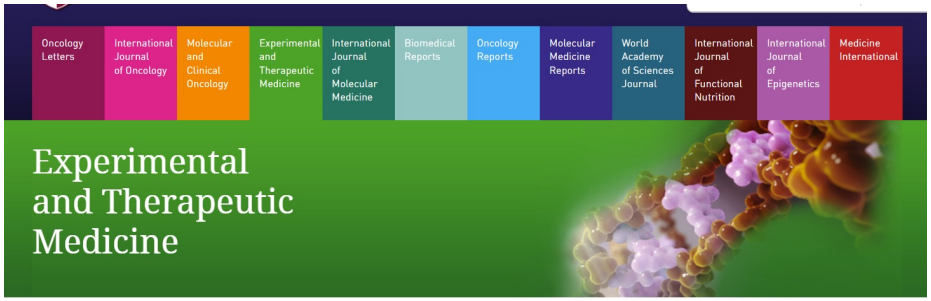
PMCID: PMC2426843 PMID: 2371184

Abstract

Anticardiolipin antibody levels were measured in 57 patients with Mycoplasma pneumoniae infection and 21 patients with other infections. Significantly more patients in the mycoplasma group had increased IgM and IgG anticardiolipin. Within the mycoplasma group significantly higher titres were found in patients with severe infection (assessed by need for hospital admission) and in patients with cold agglutinins. A tendency for particularly high titres to occur in patients with extra-pulmonary complications was identified.



3

EMERGING INFECTIOUS DISEASES®

Volume 5, Number 1—February 1999

Dispatch

Mycoplasma penetrans Bacteremia and Primary Antiphospholipid Syndrome

Antonio Yáñez*✉, Lilia Cedillo†, Olivier Neyrolles‡, Encarnación Alonso*, Marie-Christine Prévost‡, Jorge Rojas*, Harold L. Watson§, Alain Blanchard‡, and Gail H. Cassell§

Author affiliations: *Centro de Investigación Biomédica de Oriente-IMSS, Puebla City, Mexico;; †Benemérita Universidad Autónoma de Puebla, Puebla City, Mexico;; ‡Institut Pasteur, Paris, France;; §University of Alabama at Birmingham, Birmingham, Alabama, USA

Cite This Article

Abstract

Mycoplasma penetrans, a rare bacterium so far only found in HIV-infected persons, was isolated in the blood and throat of a non-HIV-infected patient with primary antiphospholipid syndrome (whose etiology and pathogenesis are unknown).

Antiphospholipid syndrome (APS), first described in 1983 to 1986, is characterized by a wide variety of hemocytopenic and vaso-occlusive manifestations and is associated with antibodies directed against negatively charged phospholipids. Features of APS include hemolytic anemia, thrombocytopenia, venous and arterial occlusions, livedo reticularis, pulmonary manifestations, recurrent fetal loss, neurologic manifestations (stroke, transverse myelitis, Guillain-Barré syndrome); and a positive Coombs test, anticardiolipin antibodies, or lupus anticoagulant activity (1). The factor(s) causing production of the antiphospholipid antibodies in primary antiphospholipid syndrome (PAPS) remain unidentified (2).

A substantial number of patients with *Mycoplasma pneumoniae*–induced respiratory disease have anticardiolipin antibodies (3). Furthermore, many clinical criteria for APS have also been well documented in patients with *M. pneumoniae* infection, including Guillain-Barré–like illness and other central nervous system manifestations, hemolytic anemia, positive Coombs test, thrombocytopenia, and arthritis (4).

Antiphospholipid antibodies

Certain studies and case reports have demonstrated that patients with thrombosis secondary to *Mycoplasma pneumoniae* infection were positive for anticardiolipin antibodies, Β2-glycoprotein antibodies or lupus anticoagulant antibodies (28,32,46,51,53,54). These aforementioned antibodies were transient and became negative in certain patients 3-6 months after initial disease onset (28,32,46,53,54). Anticardiolipin antibody, Β2-glycoprotein antibody and lupus anticoagulant antibody are all antiphospholipid antibodies, which reacts to phospholipids, phospholipid-protein complexes and phospholipid-binding proteins (75,76). The antiphospholipid antibodies contribute toward the formation of a thrombus (76). Antiphospholipid antibodies cause thrombosis through protein phosphatase 2A activation via apolipoprotein E receptor 2, disabled-2 and src homology domain-containing transforming protein 1 complex formation in the endothelium (77). Patients with thrombosis and positive antiphospholipid antibodies are also likely to develop thrombosis again (78).

3

Source: 1. Snowden N et al. Antiphospholipid antibodies and Mycoplasma pneumoniae infection. Postgrad Med J. 1990 May;66(775):356-62.;
2. Yáñez A et al. Mycoplasma penetrans bacteremia and primary antiphospholipid syndrome. Emerg Infect Dis. 1999 Jan-Feb;5(1):164-7; 3. Liu J, Li Y. Thrombosis associated with *mycoplasma pneumoniae* infection (Review). Exp Ther Med. 2021 Sep;22(3):967.

Strep has also been associated: might APS be a cofactor in PANDAS and other basal ganglia encephalitic disorders?

Strep

J Immunol Res. 2014 Mar 13;2014:239398. doi: 10.1155/2014/239398

Revisiting the Molecular Mechanism of Neurological Manifestations in Antiphospholipid Syndrome: Beyond Vascular Damage

M Carecchio [1,*], R Cantello [1], C Comi [1,2]

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Abstract

Antiphospholipid syndrome (APS) is a multiorgan disease often affecting the central nervous system (CNS). Typically, neurological manifestations of APS include thrombosis of cerebral vessels leading to stroke and requiring prompt initiation of treatment with antiplatelet drugs or anticoagulant therapy. In these cases, alterations of the coagulation system at various levels caused by multiple effects of antiphospholipid antibodies (aPL) have been postulated to explain the vascular damage to the CNS in APS. However, several nonvascular neurological manifestations of APS have progressively emerged over the past years. Nonthrombotic, immune-mediated mechanisms altering physiological basal ganglia function have been recently suggested to play a central role in the pathogenesis of these manifestations that include, among others, movement disorders such as chorea and behavioral and cognitive alterations. Similar clinical manifestations have been described in other autoimmune CNS diseases such as anti-NMDAR and anti-VGCK encephalitis, suggesting that the spectrum of immune-mediated basal ganglia disorders is expanding, possibly sharing some pathophysiological mechanisms. In this review, we will focus on thrombotic and nonthrombotic neurological manifestations of APS with particular attention to immune-mediated actions of aPL on the vascular system and the basal ganglia.

"Streptococcal infections may also be associated with increased aCL titers, mainly IgG isotypes, in acute post-streptococcal glomerulonephritis and streptococcal impetigo without renal involvement"[1]

Source: Ilarraza H et al. Anticardiolipin antibodies are not associated with rheumatic heart disease. Lupus. 2001;10:873–5.

Chronological association of APS improvement and eradication of H. pylori suggests role of this chronic bacterial infection

H pylori

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Helicobacter Pylori Infection and Antiphospholipid Antibodies Syndrome: A Case Report and Meta-Analysis of the World Literature

Figura N[1]*, Moretti E[1], Collodel G[2], Langone F[2], Fiorilli G[1], Campagna M[1], Giordano N[1], Gonnelli S[1], Nuti R[1]

[1]Department of Medical, Surgical and Neurological Sciences, University of Siena, Siena, Italy
[2]Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy

*Corresponding author: Natale Figura, Associate Professor of Gastroenterology, Department of Medical, Surgical and Neurological Sciences, University of Siena, vialeBracci 8, 53100 Siena, Italy, Tel: +39 0577585463; E-mail: natale.figura@unisi.it

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Introduction

Helicobacter pylori infection is one of the most common chronic infective conditions in the world, present in more than the 50% of the global population [1]. *H. pylori* are a gram-negative helix-shaped bacterium, microaerophilic not sporigen and urease-positive, which colonizes the gastric mucosa, inducing chronic gastritis and peptic ulcer. *H. pylori* infection also concurs to the development of gastric mucosa atrophy, intestinal metaplasia and gastric cancer, such as adenocarcinoma and gastric MALT lymphoma [1-3]. Recent studies have shown that the infection can be related to many extra gastric conditions, such as ischemic heart disease, stroke, neurologic (Alzheimer and Parkinson), endocrine (diabetes mellitus, autoimmune thyroiditis), hematologic (iron deficiency anemia, immune thrombocytopenic purpura), dermatologic (chronic urticaria, acnes rosacea) diseases and infertility [4,5].

The pathogenicity of *H. pylori* is modulated by many virulence factors, in particular the vacuolating cytotoxin VacA and the cytotoxin-associated gene A on coprotein CagA, which is expressed by the homologous gene present in the *cag* pathogenicity island. CagA is an important factor even in the development of extra-gastric manifestations, acting through autoimmune or pro-inflammatory pathways [4].

Antiphospholipid syndrome (APS) (also known as Hughes syndrome) is an autoimmune disease characterized by hypercoagulability, recurrent miscarriage and arterial and venous thrombosis. Diagnostic criteria of APS include the positivity for circulating levels of LAC (Lupus Anti-Coagulant) antibodies, Anti-b2 glycoprotein-I (IgG and/or IgM isotype) and cardiolipin antiphospholipid antibodies [6,7]. This syndrome could be primary (*i.e.* isolated) or secondary to rheumatologic

the Cochrane Database of Systematic Reviews, Premedline, Healthstar, by using the MeSH heading: "Helicobacter pylori", "H. pylori", "H pylori", "Campylobacter pylori", "C. pylori", "C pylori", "infection", AND ("antibodies, antiphospholipid" OR ("antibodies"[All Fields] AND "antiphospholipid" [All Fields]) OR "antiphospholipid antibodies" [All Fields] OR ("phospholipid" [All Fields] AND "antibody" [All Fields]) OR "phospholipid antibody" [All Fields]).

At the current time, we found only one example in literature supporting the relationship between *H. pylori* and APS. Cicconi et al. [8], reported a case of 33-years old woman, affected by APS and positive for *H. pylori* infection. In this case, authors found a positive titer for antiphospholipid IgM, related with *H. pylori* infection confirmed by Urea Breath Test. The patient's symptoms were left sided hemiparesthesias with episodic arms weakness, treated with nimodipine and aspirin for six months without benefits. The antiphospholipid titer decreased after successful *H. pylori* eradication therapy (clarithromycin 500 mg bid + metronidazole 250 mg bid + omeprazole 20 mg die for seven days), with a gradual symptoms remission.

In April 2003, we observed in our department a 47 year-old woman with an history of recurrent miscarriage (three episodes) and an event of amaurosis. The patient was admitted to our structure for dizziness, nausea and hypotension. Cerebral-CT and MRI showed an obliteration

"We hypothesise that H. pylori infection could concur to determine the development of APS through two possible mechanisms: … antigenic mimicry between bacterial and artery antigens and the chronic stimulation of inflammatory cytokines, which … takes place when the infecting organisms express CagA."

Source: Figura et al. (2015). Helicobacter Pylori Infection and Antiphospholipid Antibodies Syndrome: A Case Report and Meta-Analysis of the World Literature.

Agenda

- Mechanism by which infections can trigger antiphospholipid antibodies/syndrome
- Viral involvement
- Bacterial involvement
- Infections indicated

Antiphospholipid Syndrome

Infections that may be involved

1. CMV/EBV
2. Mycoplasma pneumoniae
3. HIV
4. Hepatitis B and C
5. Parvovirus B19
6. H pylori
7. SARS-CoV-2 infection & vaccination

Small selection

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