Presence of Immune Complexes of IgG/IgM bound to β_2-glycoprotein-I is associated with non-criteria manifestations in antiphospholipid syndrome

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APSFORUMMAASTRICHT

Disclosures

- None

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FACTS

Currently, several authors have been emphasizing the need for new APS biomarkers to improve sensitivity and specificity in the diagnosis of the syndrome.

Cervera R, Serrano R, Pons-Estel GJ, Ceberio-Hualde L, Shoenfeld Y, de Ramon E, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis (2015) 74(6):1011-8.

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FACTS

Presence of immune complexes of IgA aβ_2GPI antibodies bound to β_2A-CIC has been described recently in the blood of patients with clinical thrombotic manifestations in APS.

Martinez-Flores JA, Serrano M, Perez D, Camara AG, Lora D, Morillas L, et al. Circulating Immune Complexes of IgA Bound to Beta 2 Glycoprotein are Strongly Associated with the Occurrence of Acute Thrombotic Events. J Atheroscler Thromb (2016) 23(10):1242-53.

FACTS

However, prevalence in APS patients of circulating immune complexes between aPL and β_2-CIC, and the relationship of these complexes with other APS clinical manifestations have still not been described.

THE AIM

- **To determine the possible prevalence of β_2-CIC of IgG and/or IgM isotypes (β_2G-CIC and β_2M-CIC, respectively) in patients with APS and diferent clinical manifestations.**

- **A cross-sectional study developed to determine the prevalence of β_2-CIC in APS patients with thrombotic manifestations.**

Project Issued by the Ministry of Science of the Republic of Serbia

- ***Grant number 145020 for 2005-2010:***

Multidisciplinary Study of Risk Factors for the Development of Thrombosis in APS

- ***Grant number 175041 for 2011-2020:***

Multidisciplinary study of genetic and acquired abnormalities of the immune response for the occurrence of systemic antiphospholipid syndrome manifestations:

Multidisciplinary Research Team of Project

1. Dragomir Marisavljevic
2. Ljudmila Stojanovich
3. Mirjana Krotin
4. Nemanja Damjanov
5. Ivo Elezovic
6. Željko Mikovic
7. Mladenko Vasiljevic
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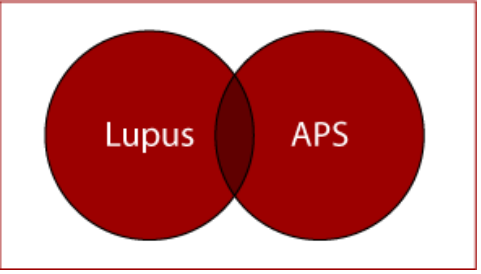
2. Institut of Rheumatology, Moskow

CCS: Clinical Center of Serbia



Patient Group Description

863 patients:

554 PAPS patients:

- **413 female and 91 male**
- **mean age 44.2 + 12.7 years**

309 SLE patients with secondary APS

- **243 female and 16 male**
- **mean age 46.9 + 15.9 years**

15 (2.2%) patients with CAPS: 7 SLE+ 8 PAPS

Stojanovich L, MD, PhD

Lupus (2011) 0, 1–8
http://lup.sagepub.com

LUPUS AROUND THE WORLD

Influence of antiphospholipid antibody levels and type on thrombotic manifestations: results from the Serbian National Cohort Study

L Stojanovich[1], O Markovic[1], D Marisavljevic[1,2], I Elezovic[3,2], N Ilijevski[4,2] and N Stanisavljevic[1]
[1]Internal medicine, "Bezanijska Kosa", University Medical Center, Belgrade, Serbia; [2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia; [3]Hematology Clinics, Clinical Center of Serbia, Belgrade, Serbia; [4]Institute of Cardiovascular Disease "Dedinje", Belgrade, Serbia

LUPUS

- ✓ **Arterial thrombosis: 51% pts**
- ✓ **Venous thrombosis: 28% pts**
- ✓ **Pregnancy loss: 41% pts**

Case Communications

Treatment of Antiphospholipid Syndrome in Pregnancy with Low Doses of Intravenous Immunoglobulin

Ljudmila Stojanovich MD PhD[1], Željko Mikovic MD PhD[2], Vesna Mandic MD PhD[2] and Dragana Popovich-Kuzmanovich MD[1]

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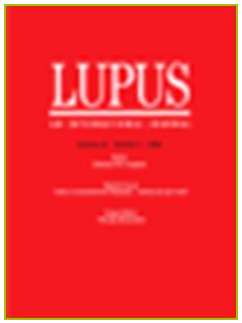
Key words: antiphospholipid syndrome, neonatal lupus, pregnancy, intravenous immunoglobulin

IMAI 2007;9:555–556

Stojanovich L, MD, PhD

Diagnostic of vascular APS manifestations

Lupus (2014) 0, 1–5
http://lup.sagepub.com



REVIEW

Tomography and blood vessels in Hughes syndrome

L Stojanovich and A Djokovic
Internal Medicine, "Bezanijska Kosa," University Medical Center, Belgrade, Serbia

- Physical examination
- X-ray diagnosis of chest
- Vascular ultrasonography (Doppler)
- Peripheral angiography
- Vascular magnetic resonance imaging/ MRA angiography
- Computed tomographic angiography (CTA)
- 64-multi slice CT - *whole body angiography*
  can allow us excellent visualization of all major and minor blood vessels

Immunol Res
DOI 10.1007/s12026-016-8887-6
NOVEL ASPECTS IN LUPUS, 2017

The role of MSCT angiography in early detection of lower limb arterial lesions in patients with antiphospholipid syndrome

Jovica Saponjski[1] · Ljudmila Stojanovich[2] · Jelena Petrovic[3] · Dusan Saponjski[4]

Autoimmunity Reviews 10 (2011) 235–237
Contents lists available at ScienceDirect
Autoimmunity Reviews
journal homepage: www.elsevier.com/locate/autrev

Review

Systemic vascular diseases in the antiphospholipid syndrome. What is the best diagnostic choice?

Jovica Saponjski *,1, Ljudmila Stojanovich 1, A. Djokovic, M. Petkovic, D. Mrda
Internal medicine, "Bezanijska Kosa", University Medical Center, Belgrade, Serbia

Association between systemic non-criteria APS manifestations and antibody type and level: results from the Serbian national cohort study

L. Stojanovich[1], M. Kontic[2], A. Djokovic[1], D. Marisavljevic[1], N. Ilijevski[3], N. Stanisavljevic[1], Z. Mikovic[4], M. Petkovic[1], V. Kovcin[1]

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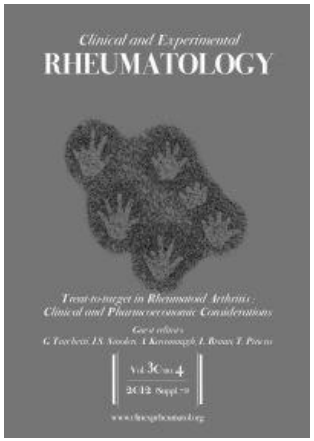
Clinical and Experimental Rheumatology 2013; 30: 1-9. ISSN 0392-856X. IF= 2.433.



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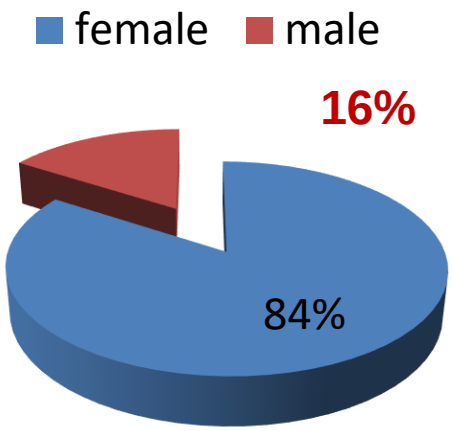
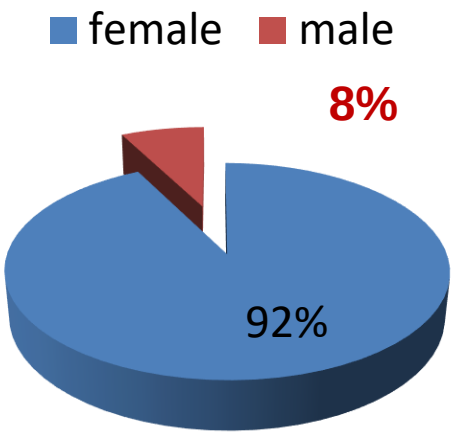
PATIENTS

57 APS PATIENTS
with thrombotic manifestations

Mean age was 47.6±1.6 years



35 PAPS



22 SAPS (SLE)

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Distribution of patients according to aPL antibody

aPL	N	%
Anti-cardiolipin IgG	24	42.1
Anti-cardiolipin IgM	25	43.9
Anti-β_2-glycoprotein I IgG	26	45.6
Anti- β_2-glycoprotein I IgM	29	50.9
Lupus anticoagulant	38	66.7
Triple aPL positivity	15	26.3

Stojanovich L, MD, PhD

Patient Group Description

CONDITION	N=57	%
Age (years)	47.6	±1.6
Sex (women)	36	63.2
Catastrophic APS	4	7.0
Primary APS	35	61.4
Disease duration (years)	5.4	±0.7
Diabetes Mellitus	2	3.5
Hypertension	5	8.8
Dyslipidemia	5	8.8
Smoker	21	36.8

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Clinical characteristics of APS patients with quadruple and triple-only aPL positivity

CONDITION	Quadruple aPL positivity			Triple-only aPL positivity		
	OR	95% CI	p	OR	95% CI	p
Livedo reticularis	12	1.1 to 133.6	0.043*	2.3	0.5 to 10.1	0.274
Leukopenia	18	1.6 to 209	0.021*	0.6	0.1 to 5.8	0.658
Thrombocytopenia	40.8	2.0 to 856	0.018*	1.1	0.2 to 6.3	0.937
Sy sicca	10.7	1.1 to 105.3	0.043*	1.1	0.1 to 11.4	0.958

*Quadruple aPL positivity: triple aPL-positivity plus of β_2-CIC

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Clinical characteristics of patients in the 2 groups

	Group 1		Group 2			
MANIFESTATION	β_2 - CIC + N = 11	%	β_2 - CIC - N = 46	%	p value	OR (95%CI)
Livedo reticularis	7	63.6	11	23.9	0.011*	5.57 (1.37-22.65)
Sy sicca	6	54.5	4	8.7	< 0.001*	12.6 (2.63-60.48)
Thrombocytopenia	6	54.6	8	17.4	0.010*	5.7 (1.39-23.36)
Leukopenia	5	45.5	6	13	0.014*	5.56 (1.28-24.03)

- Group 1: patients with circulating immune complexes of IgG or IgM bound to β_2-glycoprotein I
- Group 2: patients without circulating immune-complexes

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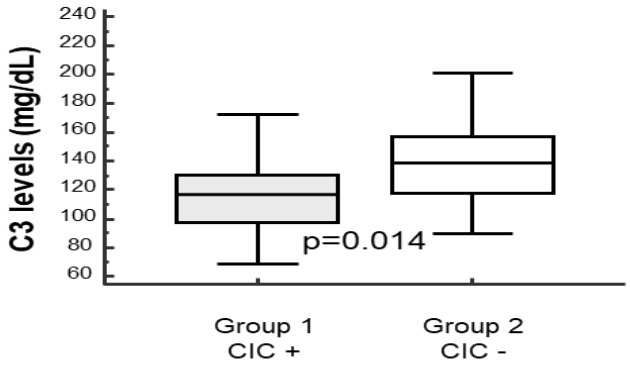
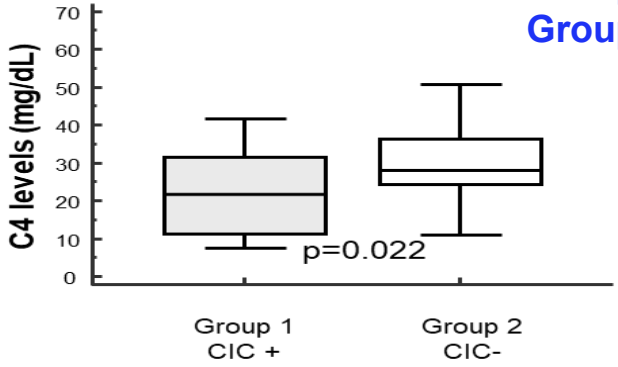
Mean levels of C3 and C4 complement in patients groups

A



B

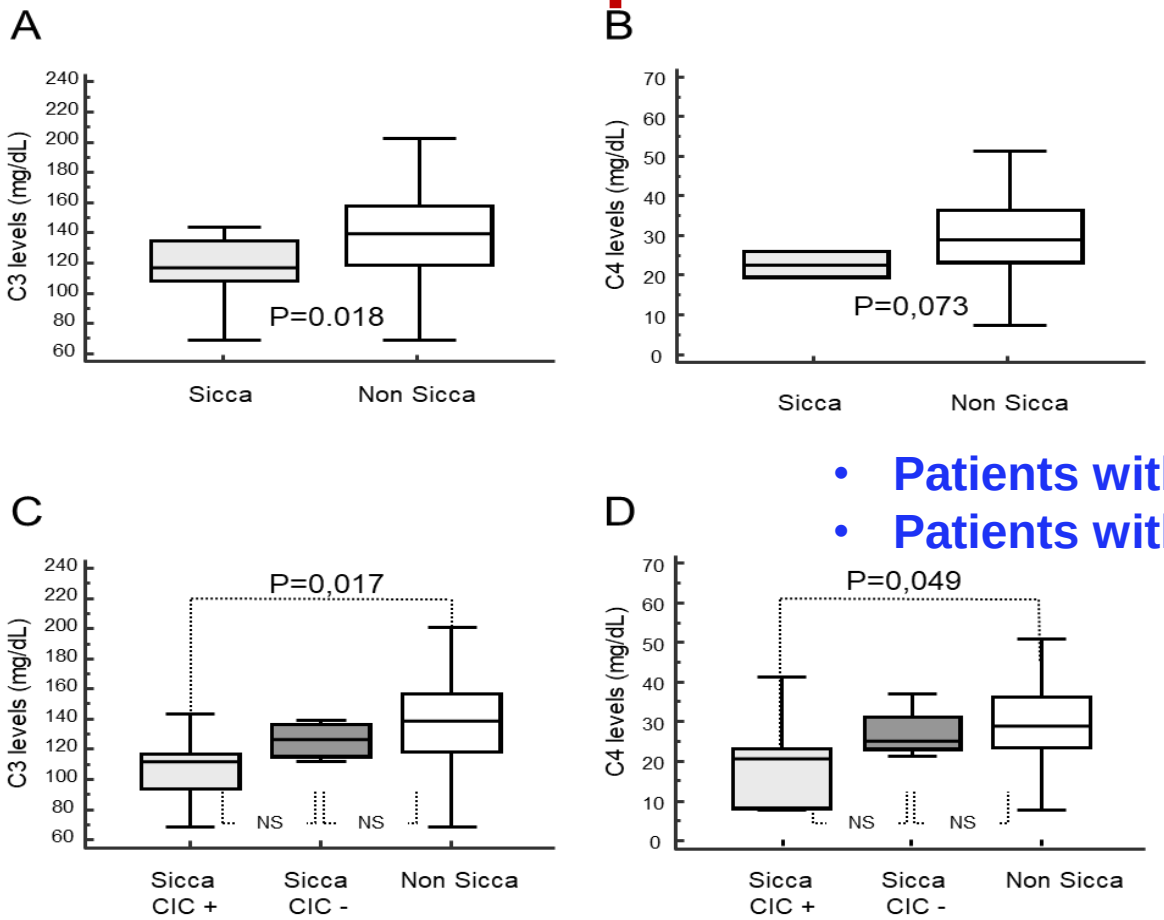


Group 1: patients with CIC of IgG or IgM bound to β_2-CIC +
Group 2: patients without CIC (β_2-CIC -)

The mean levels of C3 and C4 complement were within the normal range in both groups.

- ***C3 levels were significantly lower in group-1 than in group-2 (p=0.014)***
- ***C4 levels were decreased in group-1(p=0.022)***

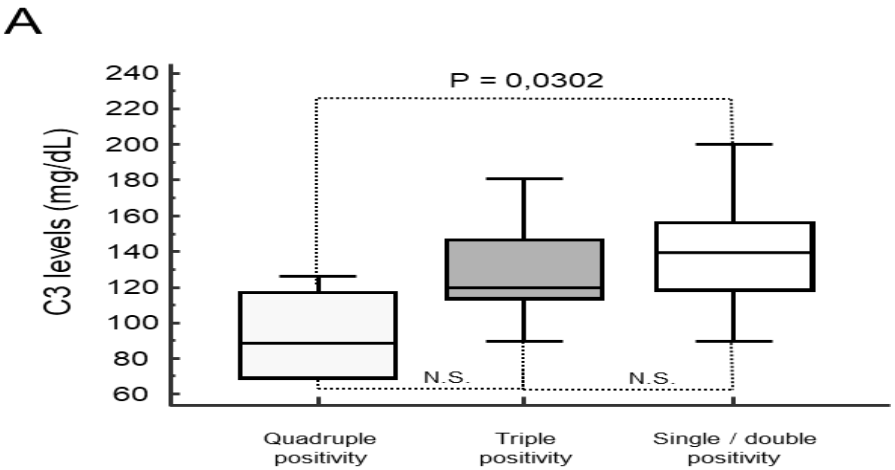
Mean levels of C3 and C4 complement in respect to sicca Sy

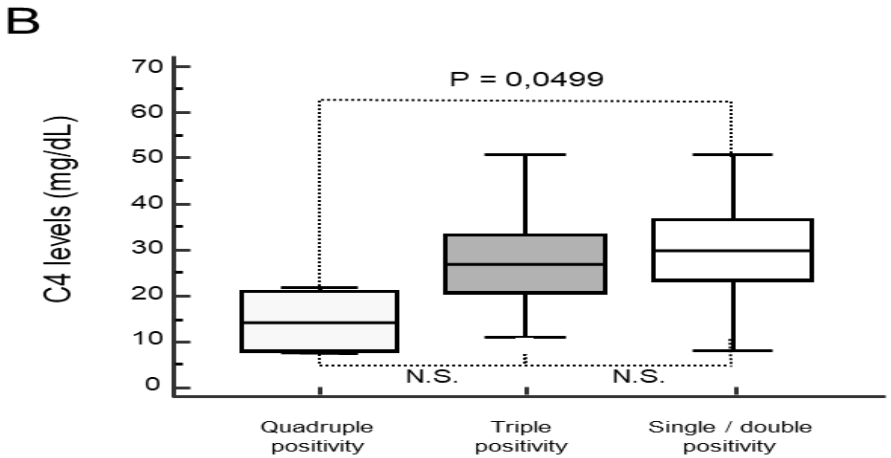


- **Patients with sicca Sy (grey box)**
- **Patients without sicca (white box)**

Levels of C3 were significantly lower in patients with sicca (p=0.014), levels of C4 were lower but the difference was not statistically significant (p=0.073).
Patients with sicca who were B2-CIC positive showed much lower C3 complement levels than patients without sicca (p=0.017). C4 complement levels were lower in patients with sicca and B2-CIC (p=0.049).

Mean levels of C3 and C4 complement in respect to aPL positivity in patients with sicca Sy





C3 (A) and C4 (B) in pts with sicca and quadruple aPL (gray) were significantly lower than patients with sicca and single/double aPL positivity(white).

Patients with triple positivity (dark) were lower, but did not significant.

- **Patients with sicca Sy (grey box)**
- **Patients without sicca (white box)**

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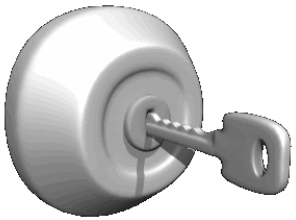


Take-home messages

- ✓ **Our study confirmed that presence of β_2-CIC is strongly associated with several non-criteria clinical APS and to higher complement consumption.**

- ✓ **There is strong link between quadruple aPL positivity (triple aPL-positivity plus of β_2-CIC) showed a higher prevalence of thrombocytopenia, leucopenia and LR than those with single/double aPL-positivity.**

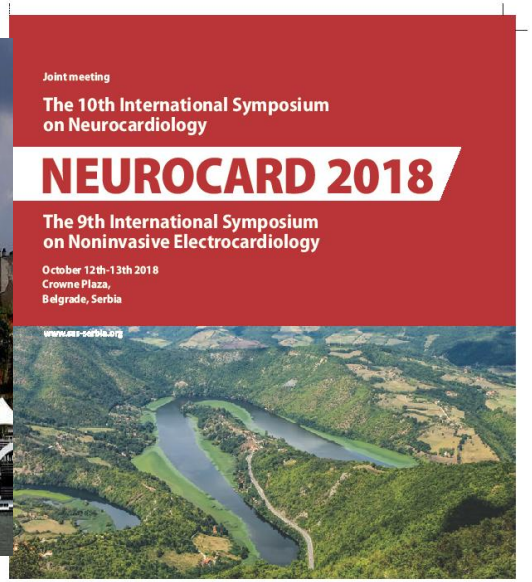
- ✓ **More studies are required to better understand the clinical significance of β_2-CIC.**

Acknowledgements

With grateful thanks to my colleagues

THANK YOU!

With love and respect, and hoping to welcome you in Belgrade very soon



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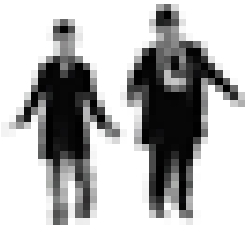

Questions?

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