Correlations between thrombotic and non-thrombotic APS manifestations

Lesions from the Serbian National Registry

Ljudmila Stojanovich

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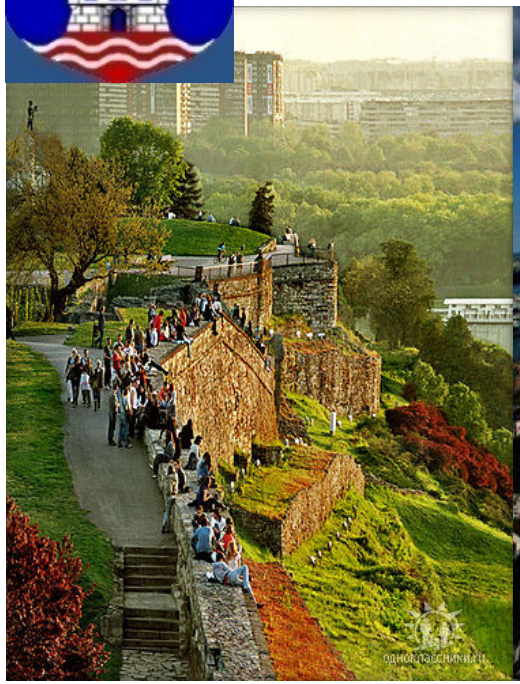
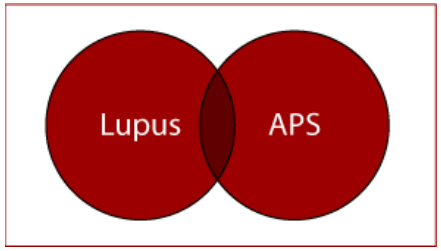
University Medical Center, Belgrade, Serbia





ANTIPHOSPHOLIPID SYNDROME

Very frequent Sy:

- ✓ 1 / 5 YOUNG WITH CVI
- ✓ 1 / 5 DVT
- ✓ 1 / 5 PREGNANCY LOSS

Stojanovich L, MD, PhD

Factors Predicting Autoimmune Diseases

Hormonal and Environmental Factors Involved in Autoimı Diseases – 2008

Yehuda Shoenfeld MD[1], Gisele Zandman-Goddard MD[2], Ljudmila Stojanovich MD[3], Maurizio
Howard Amital MD[5], Yair Levy MD[6], Mahmoud Abu-Shakra MD[7], Ori Barzilai MD[1], Yackov Be
Miri Blank PhD[9], Joselio Freire de Carvalho MD[10], Andrea Doria MD[11], Boris Gilburd PhD[9], Uri
Ilan Krause MD[12], Pnina Langevitz PhD[13], Hedi Orbach MD[14], Vitor Pordeus MD[15], Maya Ram
Elias Toubi MD[16] and Yaniv Sherer MD[1]

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Available online at www.sciencedirect.com
ScienceDirect
Autoimmunity Reviews 7 (2008) 209–213

Stress as a trigger of autoimmune disease

Ljudmila Stojanovich *, Dragomir Marisavljevich
"Bezhanijska Kosa" University Medical Center, Belgrade University, Serbia

Changeable factors

- Psychological stress
- Infection
- Vaccination
- Smoking
- Obesity
- Ultraviolet light exposure
- Drugs…

Unchangeable factors

- Genetic
- Hormonal
- Immune deficiency state
- Gender

Autoimmunity Reviews 9 (2010) A271–A276

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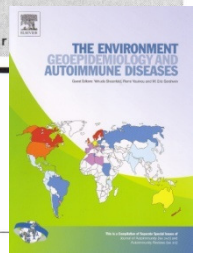
journal homepage: www.elsevier.com/locate/autr

Stress and autoimmunity

Ljudmila Stojanovich *
"Bezhanijska Kosa", University Medical Center, Belgrade University, Serbia



Sapporo Criteria on Antiphospholipid Syndrome (1998)

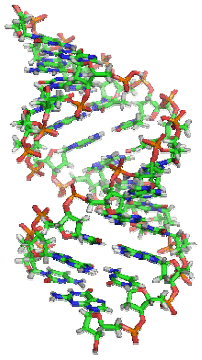
Clinical criteria

- ✓ Vascular thrombosis
- ✓ Pregnancy morbidity

Laboratory criteria

- ✓ Lupus anticoagulant
- ✓ Anticardiolipin antibody

  dependent of β_2*-GPI*



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

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

- ***Grant number 145020 for 2006-2010:***

***Multi-disciplinary Study** of Risk Factors for the Development of Thromboses in APS*

- ***Grant number 175041 for 2011-2014:***

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

Stojanovich L, MD, PhD

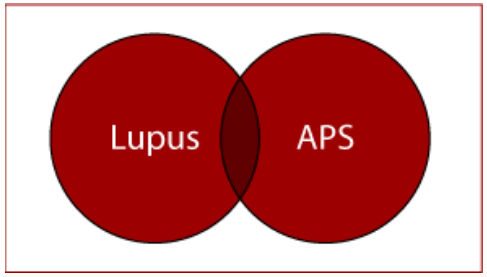
Research Goal

1. To determine prevalence and types of aPL titer (LA, ACL, β2GPI) in patients with thrombotic and non-thrombotic manifestations of the disease.
2. Analisys of gene polymorphisms that are important for the T (H) 17 and regulatory T cells differentiation in APS patients, and their corellation with the disease.
3. Determination of aPL association with the innate Thrombophilia (defficiency of AT, PC, PS, FXII, polymorphisms FV Leiden, prothrombin 20210 and MTHFR) and clinical expression.
4. Determination of aPL role in the development of induced atherosclerosis, including subclinical forms of the disease using the latest technology methods such as multi sliced computed tomography (64 MSCT), which would present the extent and location of changes in blood vessels.
5. To determine the importance of oxidative stress, markers of inflammation, endothelial adhesion receptor molecules induction and activation, as additional factors in the complicated pathophysiology and multifactorial etiology of APS thrombosis.
6. To continue in obtaining the national APS patients registry with the possibilities of its participating in international studies.
7. To overview the patient outcomes with various APS therapeutic protocols.

Stojanovich L, MD, PhD

Goals

- Aim of this study was to observe and investigate association between thrombotic and non-criteria manifestations, in prospective study of APS patients.
- Differences between patients with primary and secondary APS were also analyzed.
- This study presents the first results from our national cohort.



Patient Group Description

501/383 patients:

358/ 260 PAPS patients:

- 201 female and 59 male
- mean age 45.2 + 13.7 years

143/ 114 SLE patients with secondary APS

- 106 female and 9 male
- mean age 46.9 + 15.9 y

14 (4.5%) patients with CAPS: 7 SLE+ 7 PAPS

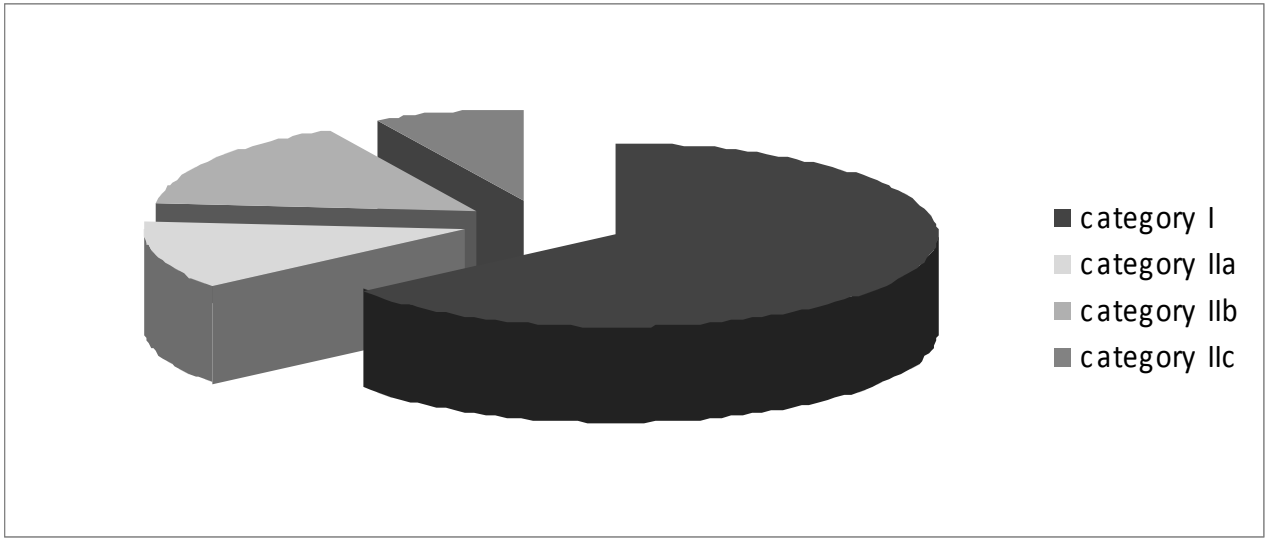
Distribution of aPL in PAPS and SAPS

Table 2. Distribution of aPL in the PAPS and SAPS groups

aPL type/ aPLcategory	PAPS (N=260)	SAPS (N=114)	p value
aCL IgG	95 (36.5)	68 (59.6)	**0.0001**
aCL IgM	141 (54.2)	73 (64.0)	**0.049**
$ß_2$GPI IgG	83 (31.9)	49 (43.0)	**0.027**
$ß_2$GPI IgM	98 (37.7)	51 (44.7)	0.122
LA	133 (51.2)	56 (49.1)	0.402
I	160 (61.5)	81 (71.1)	
IIa	41 (15.8)	5 (4.4)	
IIb	46 (17.7)	23 (20.2)	p=0.020
IIc	13 (5.0)	5 (4.4)	

Legend: PAPS= primary antiphospholipid syndrome, SAPS= secondary antiphospholipid syndrome, aCL= anticardiolipin antibodies, $ß_2$ GPI=anti- $ß_2$ glycoprotein I antibodies, LA= lupus anticoagulant, aPL= antiphospholipid antibodies
Categories: I-more than one aPL present, IIa LA present alone, IIb-aCL present alone, IIc- anti-β2GPI present alone

Distribution of patients according to antibody category



- More than one type of antibodies (category I) was present in 64.5%
- Lupus anticoagulant was present alone in 12.1% patients (category IIa)
- aCL antibodies were present alone in 16% patients (category IIb)
- anti-β2GPI antibodies were present alone in 7.4% patients (category IIc)

PengoV et al.
Antibody profiles for the diagnosis of APS.
Thromb Haemost 2005

Results
APS Manifestations

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

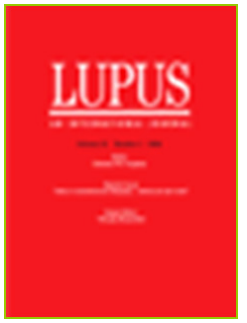
Diagnostic of vascular APS manifestations

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

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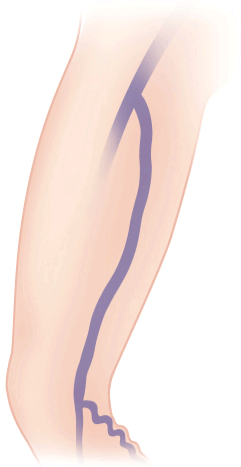
journal homepage: www.elsevier.com/locate/autrev

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

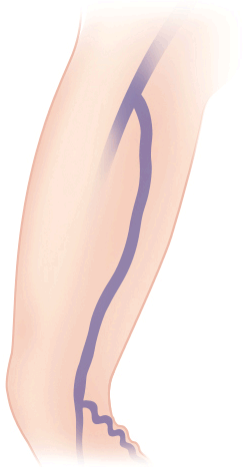


Thrombosis

Thrombosis was diagnosed:

- ✓ 83 (51.2%) PAPS patients
- ✓ 36 (38.3%) SLE patients

p = 0.045



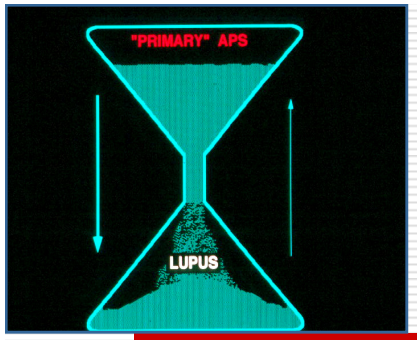
Results

- ✓ Arterial Thrombosis : 51% pts
- ✓ Venous thrombosis: 28% pts

Arterial Thrombosis

- ✓ 35% PAPS patients
- ✓ 34% SLE patients

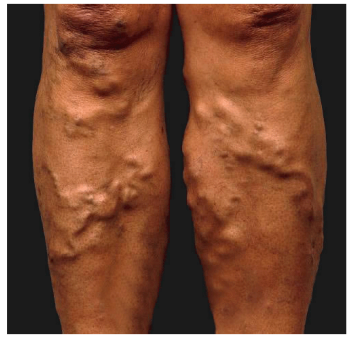
p = 0.932



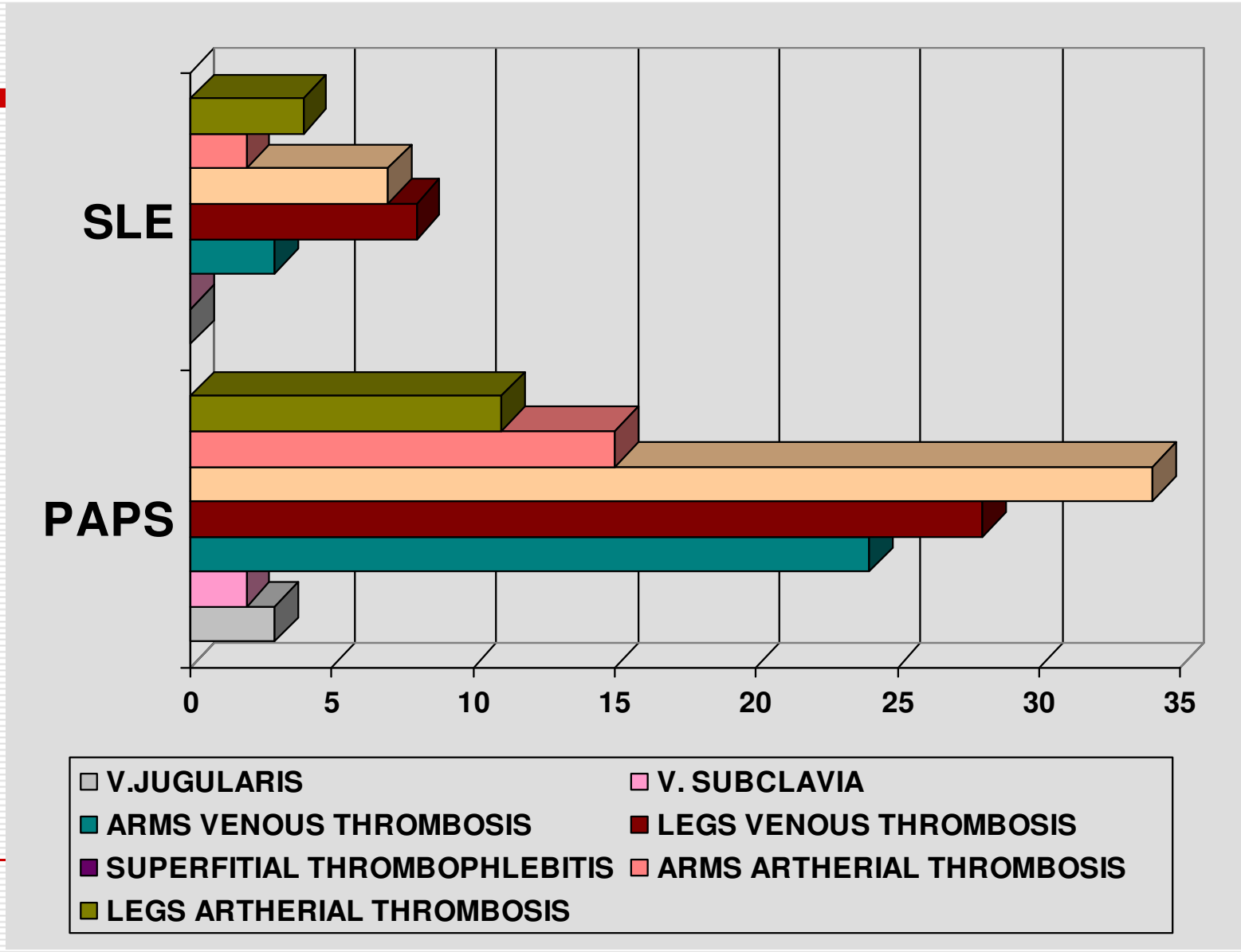
Venous thrombosis

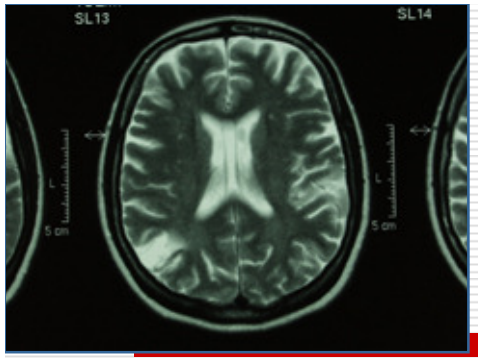
- ✓ 25.9% PAPS patients
- ✓ 8.5% SLE patients

p = 0.001



Incidence of thrombosis in APS pts in Serbia



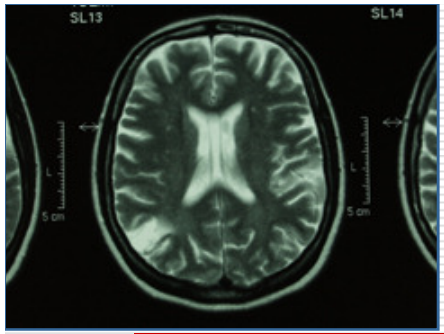


CVI in PAPS

There was a correlation between:

CVI and:

- pts with $ß_2$GPI-IgM *p=0.008*
- pts with LA *p=0.009*

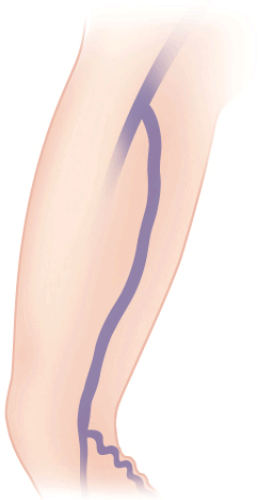


CVI in SLE

There was a correlation between:

CVI and:

- ✓ pts with $ß_2$GPI — *p=0.008*
- ✓ pts with LA — *p=0.009*

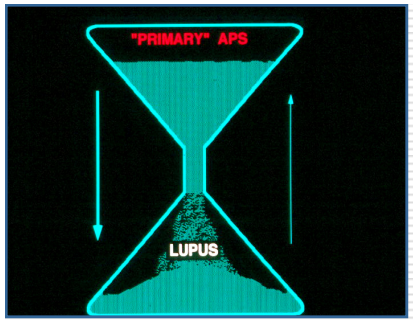


Analysis of aPL and localization of thrombosis

There was no correlation between:

other localization of arterial thrombosis and the type of aPL

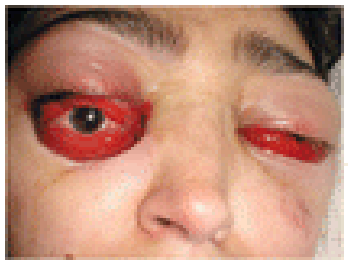
$p > 0.05$



Thrombosis in PAPS was significantly more frequent than in SLE:

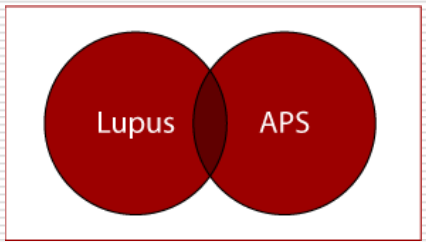
- ✓ superior extremity *p=0.004*
- ✓ inferior extremity deep vein *p=0.027*
- ✓ inferior extremity superficial thrombophlebitis *p=0.004*

Analysis of aPL and localization of thrombosis



- ✓ aCL-IgM and cerebral venous sinus thrombosis
- ✓ aCL-IgM and jugular venous thrombosis

p= 0.040



Analysis of aPL and localization of thrombosis

There was no correlation between:

other localization of venous thrombosis and the type of aPL

$p > 0.05$

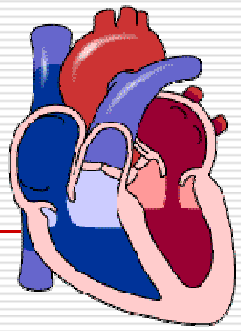
Distribution of arterial and venous thrombosis in PAPS and SAPS patients under and over 45 years of age

Age	PAPS		Secondary APS	
	AT	VT	AT	VT
≤45 years	17 (28.5%)	20 (24.15%)	14 (25.5%)	4 (7.3%)
>45 years	39 (49.2%)	22 (27.8%)	18 (46.2%)	4 (10.3%)
	p=0.028	p=0.238	p=0.031	p=0.439

Analysis of localization of thrombosis and age

Age was a significant risk factor for:

- CVI: 51.92 and 41.97 years, respectively p=0.001
- MI: 56.6 and 43.6 years, respectively p=0.0001



Analysis of activity of SLE (SLEDAI) and thrombosis

The median SLEDAI score was 9 in patients without thrombosis.

The median SLEDAI score was 13.5 in patients with thrombosis.

p=0.03

The activity of SLE was in significant correlation with the prevalence of thrombosis.

Distribution of aCL IgG/IgM levels in PAPS patients with arterial and venous thrombosis

PAPS	Level of aCL IgG				Level of aCL IgM			
	Low	medium	high	p	low	medium	high	p
Thrombosis %	50.0	65.2	46.7	0.520	60.6	56.3	37.9	0.069
AT	33.3	52.2	26.7	0.253	45.1	28.1	25.9	0.095
VT	25.9	26.1	26.1	0.553	28.2	37.5	17.2	0.195

Distribution of aCL IgG/IgM levels in SAPS patients with arterial and venous thrombosis

Secondary APS	Level of aCL IgG				Level of aCL IgM			
	low	medium	high	p	low	medium	high	P
Thrombosis %	29.8	37.5	51.6	0.256	26.7	35.5	51.5	0.094
AT	25.5	37.5	45.2	0.298	26.7	25.8	48.5	0.119
VT	4.3	0	19.4	0.054	6.7	12.9	6.1	0.484

Distribution of β2GP1 IgG/IgM levels in patients with PAPS

PAPS	β2GPI-IgG				2GPI-IgGM			
	low	medium	high	p	low	medium	high	p
Thrombosis %	50.0	65.2	46.7	0.882	48.9	42.9	64.1	0.201
AT	33.3	52.2	26.7	0.898	30.9	28.6	48.7	0.088
VT	25.9	26.1	26.7	0.973	27.7	17.9	28.2	0.645

Distribution of β2GP1 IgG/IgM levels in patients with SAPS

Secondary APS	β2GPI-IgG				β2GPI-IgGM			
	low	medium	high	p	low	medium	high	p
Thrombosis %	32.7	33.3	50.0	0.270	42.6	33.3	34.8	0.275
AT	28.8	25.0	46.7	0.107	40.4	25	30.4	0.298
VT	9.6	8.3	6.7	0.952	8.5	12.5	4.3	0.324

Comparisons between Pulmonary Manifestations and Gender in PAFS

	Male N=54	Female N=159	p
Pulmonary embolism and infarction	18.5%	13.2%	0.464
Primary pulmonary hypertension	1.9%	1.3%	0.999
Secondary pulmonary hypertension	13%	3.2%	0.019*
Major pulmonary arterial thrombosis	3.7%	1.9%	0.814
Pulmonary microthrombosis	24.1%	13.3%	0.099
Acute respiratory distress syndrome	5.6%	1.3%	0.203

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Autoimmunity Reviews 5 (2006) 344–348

AUTOIMMUNITY REVIEWS
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Review

Pulmonary manifestations in antiphospholipid syndrome

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Received 18 January 2006; accepted 6 February 2006
Available online 3 March 2006

Comparisons between Pulmonary Manifestations and Gender in SAFS

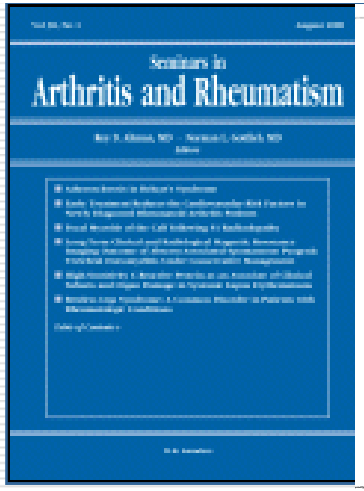
	Male N=13	Female N=99	P
Pulmonary embolism and infarction	15.4%	7.1%	0.621
Primary pulmonary hypertension	0	0	/
Secondary pulmonary hypertension	0%	2%	0.999
Major pulmonary arterial thrombosis	0%	2%	0.999
Pulmonary microthrombosis	23.1%	6.1%	0.114
Acute respiratory distress syndrome	0%	3%	0.999

Scand J Rheumatol 2012;iFirst article:1–4

Pulmonary events in antiphospholipid syndrome: influence of antiphospholipid antibody type and levels

L Stojanovich[1], M Kontic[2], A Djokovic[1], N Ilijevski[3], N Stanisavljevic[1], D Marisavljevic[1]

[1]Internal Medicine, 'Bezanijska Kosa', University Medical Centre, Belgrade, [2]Pulmonology Clinic, Clinical Centre of Serbia, University in Belgrade, and [3]Institute of Cardiovascular Disease 'Dedinje', Belgrade, Serbia

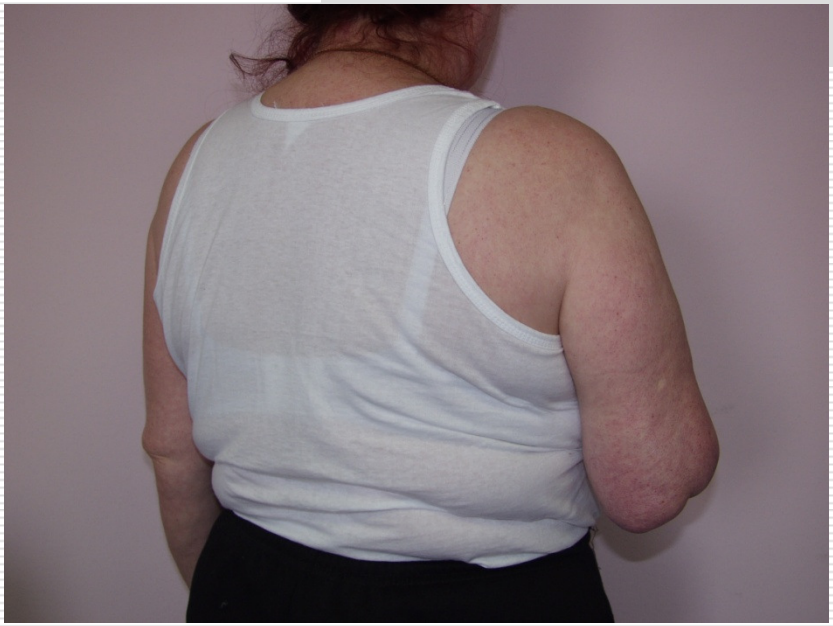


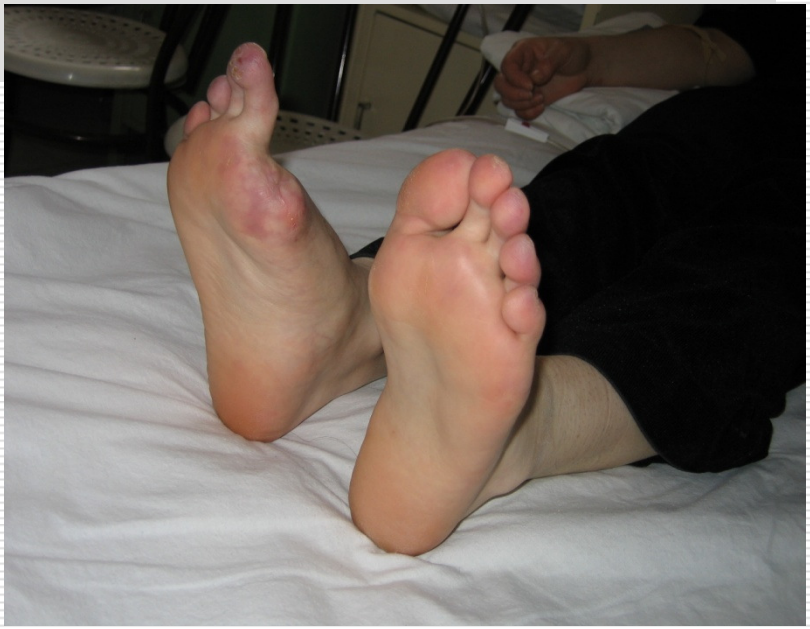
VASCULITIS AND VASCULOPATHY

Amputation of Digits or Limbs in Patients with Antiphospholipid Syndrome

Ronald A. Asherson, MD, FACP, FRCP,*
Ricard Cervera, MD, PhD, FRCP,† Evandro Klumb, MD,‡
Ljudmila Stojanovic, MD,§ Piercarlo Sarzi-Puttini, MD,¶ Janet Yinh, MD,‖
Silvia Bucciarelli, MD, PhD,† Gerard Espinosa, MD, PhD,†
Roger Levy, MD,** and Yehuda Shoenfeld, MD, FRCP††

Digital gangrene/with amputations





Stojanovich L, MD, PhD

Wrapping up

- ✓ Thrombosis was diagnosed with higher prevalence in PAPS compared to SLE patients
- ✓ Patients over 45 years of age were at a higher risk for arterial thrombosis, particularly for cerebral ischemic attack and myocardial infarction.

Wrapping up

- ✓ LA positivity was a risk factor for deep venous thrombosis and CVI in PAPS patients, and for CVI and pulmonary embolism in SLE patients.
- ✓ The activity of SLE (SLEDAI) was in significant correlation with the prevalence of thrombosis.

Wrapping up

- ✓ The prevalence of thrombosis was similar in all antibody category groups. Any aPL level and type is risk factor for thrombotic event in ours APS patients.
- ✓ After 10 years follow-up, we observed no thrombotic manifestations in any patients with high aPL levels. *All patients were treated according to international protocols*

Lupus (2011) 0, 1–8

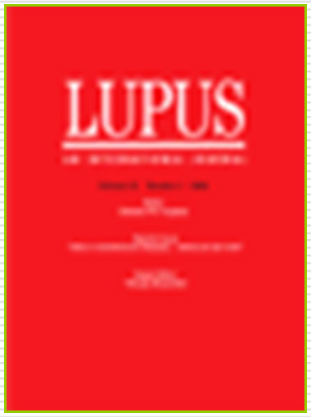
http://lup.sagepub.com

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

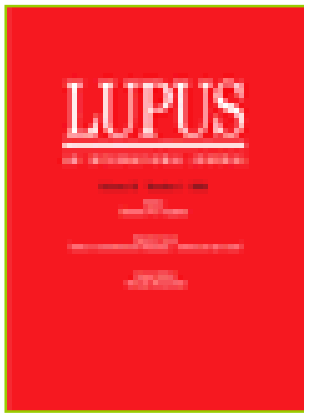


Systemic APS by Shoenfeld Y

Lupus. 2003

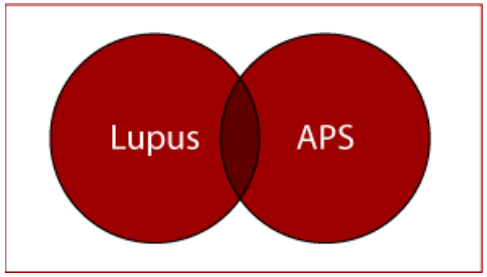
1) Skin (livedo reticularis)
2) Heart (non-verrucal endocarditis)
3) Kidneys (renal artery stenosis)
4) Circulation (hypertension, atherosclerosis)
5) Lung (pulmonary hypertension)
6) Brain (cognitive impairment)
7) Brain Vasculature (migraine)
8) Blood elements (AIHA, thrombocytopenia)
9) Bones (osteonecrosis)
10) Adrenals (apoplexy)
11) Placenta (insuficiency, fetal death)
12) Pregnancy (eclampsia, pregnansy loss)
13) Coagulation (hypercoagulable state)
14) Blood vessels (accelerated atherosclerosis)
15) Eyes (amaurasis fugox, optic neuritis)
16) Ears (acute hearing loss)
17) GI involvement (spleen, Budd Chiari)

Stojanovich L, MD, PhD



Methods

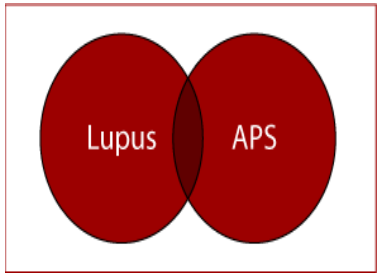
- ✓ Cardiac non-thrombotic manifestations
- ✓ Neurological non-thrombotic manifestations
- ✓ Skin non-thrombotic manifestations
- ✓ Hematological



Results

Table 1. Prevalence of non-thrombotic manifestations in patients with primary and secondary APS

Non-criteria manifestations	PAPS (N=260)	SAPS (N=114)	p-value
Epilepsy	5 (8.4)	21 (18.4)	p=0.0001
Chorea	0 (0)	9 (7.9)	p=0.0001
Livedo reticularis	34 (13.1)	76 (66.7)	p=0.0001
Pseudovasculitis	33 (12.7)	68 (59.6)	p=0.0001
Skin ulcerations	25 (9.6)	40 (35.1)	p=0.0001
Thrombocytopenia	43 (16.5)	44 (38.6)	p=0.0001
Valve thickening and dysfunction	9 (3.5)	7 (6.1)	p=0.182



Incidence of non-criteria manifestations in pts with/without LA

Non-criteria manifestation	PAPS			SAPS		
	Negative %	Positive %	p value	Negative %	Positive %	p value
Epilepsy	8.0	5.7	0.397	17.0	17.0	0.608
Migraine	33.3	24.1	0.132	42.6	27.7	0.097
Chorea	/	/	/	6.4	12.8	0.243
Dementia	11.5	3.4	0.038*	17.0	12.7	0.773
Livedo reticularis	16.0	10	0.272	34	28	0.138
Pseudovasculitis	11	14	0.383	33	23	0.058
Skin ulcerations	6	8	0.506	13	17	0.254
Thrombocytopenia	7	18	0.036*	16	21	0.199

Stojanovich L, MD, PhD

Distribution of non-criteria manifestation according to different aPL levels in APS pts

Level of aCL IgG	Low (%)	Medium (%)	High (%)	p
Epilepsy	7.4	24.8	7.4	0.021
Thrombocytopenia	29.0	11.3	17.8	0.001
Level of aCL IgM				
Epilepsy	33.3	22.2	14.8	0.032
Skin ulcerations	34.1	15.9	6.8	0.013
Level of β_2GPI IgG				
Dementia	22.2	25.9	3.7	0.047
Thrombocytopenia	27.4	14.5	11.3	0.001
Level of β_2GPI IgM				
Pseudovasculitis	39.5	2.5	8.6	0.017
Skin ulcerations	29.5	4.5	11.4	0.044

Stojanovich L, MD, PhD

Distribution of pts with PAPS according to aCL-IgG levels

	Negative %	*Low %*	*Medium %*	*High %*	p
Vegetations	60.1	26.6	13.3	0	1.0
Pseudoinfective endocarditis	40.0	60.0	0	0	0.547
Non stable angina	61.9	28.6	9.5	0	0.588
Coronary bypass occlusion	50.0	50.0	0	0	0.312
Epilepsy	81.8	9.1	9.1	0	0.494
Migraine	65.2	23.9	10.7	0	0.530
Dementia	76.9	15.4	7.7	0	0.645
Livedo reticularis	60.0	20.0	4.0	4.0	0.013*
Pseudovasculitis	20.0	38.5	7.7	0	0.680
Skin ulceration	18.7	14.2	7.1	0	0.645
Thrombocytopenia	56.0	20.0	8.0	16.0	0.001*

Stojanovich L, MD, PhD

Distribution of pts with PAPS according to aPL levels

Level of aCL IgG	N (present)	Low	Medium	High	p
Livedo reticularis	22	22.7%	4.6%	4.6%	0.013
Thrombocytopenia	25	20.0%	8.0%	16.0%	0.001
Level of β_2GPI IgG					
Thrombocytopenia	25	24.0%	12.0%	20.0%	0.0003
Level of β_2GPI IgM					
Migraine	45	41.3%	4.3%	2.2%	0.003

Stojanovich L, MD, PhD

Distribution of pts with SAPS according to aPL levels

aPL		Low	Medium	High	p
Level of aCL IgM	N (present)				
Skin ulcerations	30	40.0%	20.0%	16.7%	0.049
Level of β_2GPI IgG					
Chorea	9	44.4%	44.4%	11.1%	0.008
Level of β_2GPI IgM					
Chorea	9	22.2%	33.3%	11.1%	0.047
Livedo reticularis	62	38.7%	3.2%	8.1%	0.008
Pseudovesculitis	54	39.3%	3.6%	10.7%	0.032
Thrombocytopenia	37	21.6%	8.1%	8.1%	0.001

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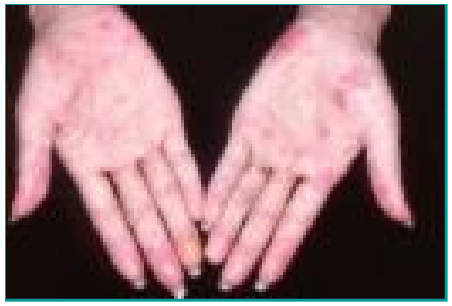
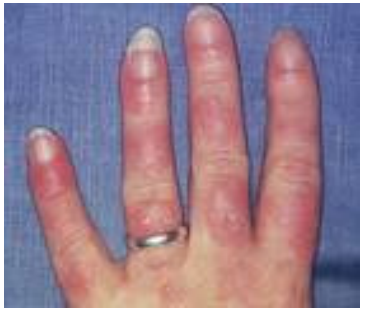
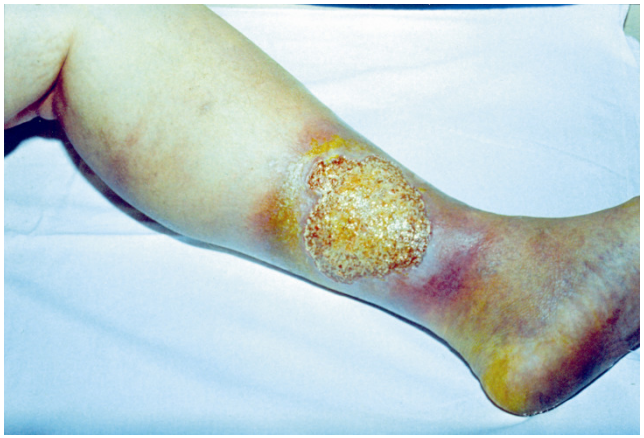


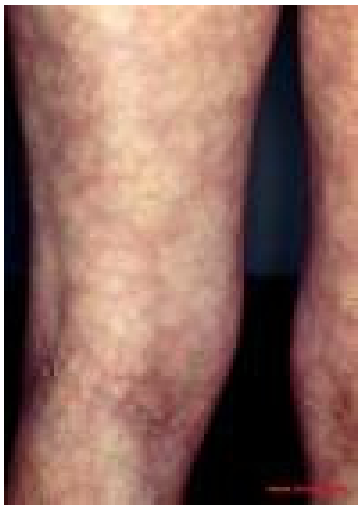
Methodology

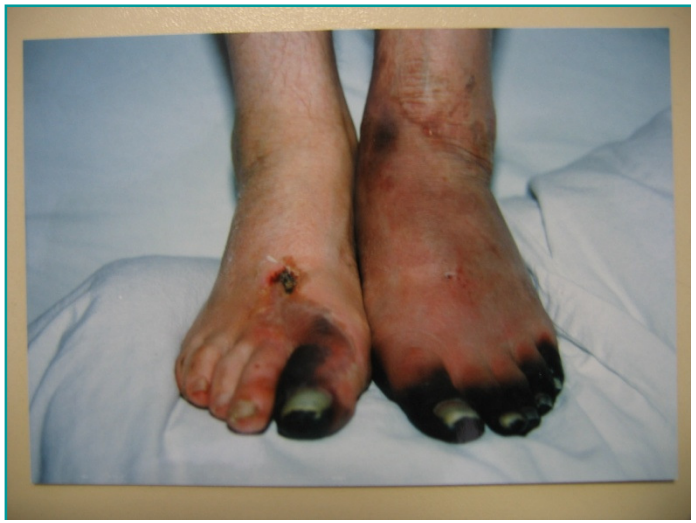


In all patients, clinical observation was performed to reveal the presence of skin manifestations

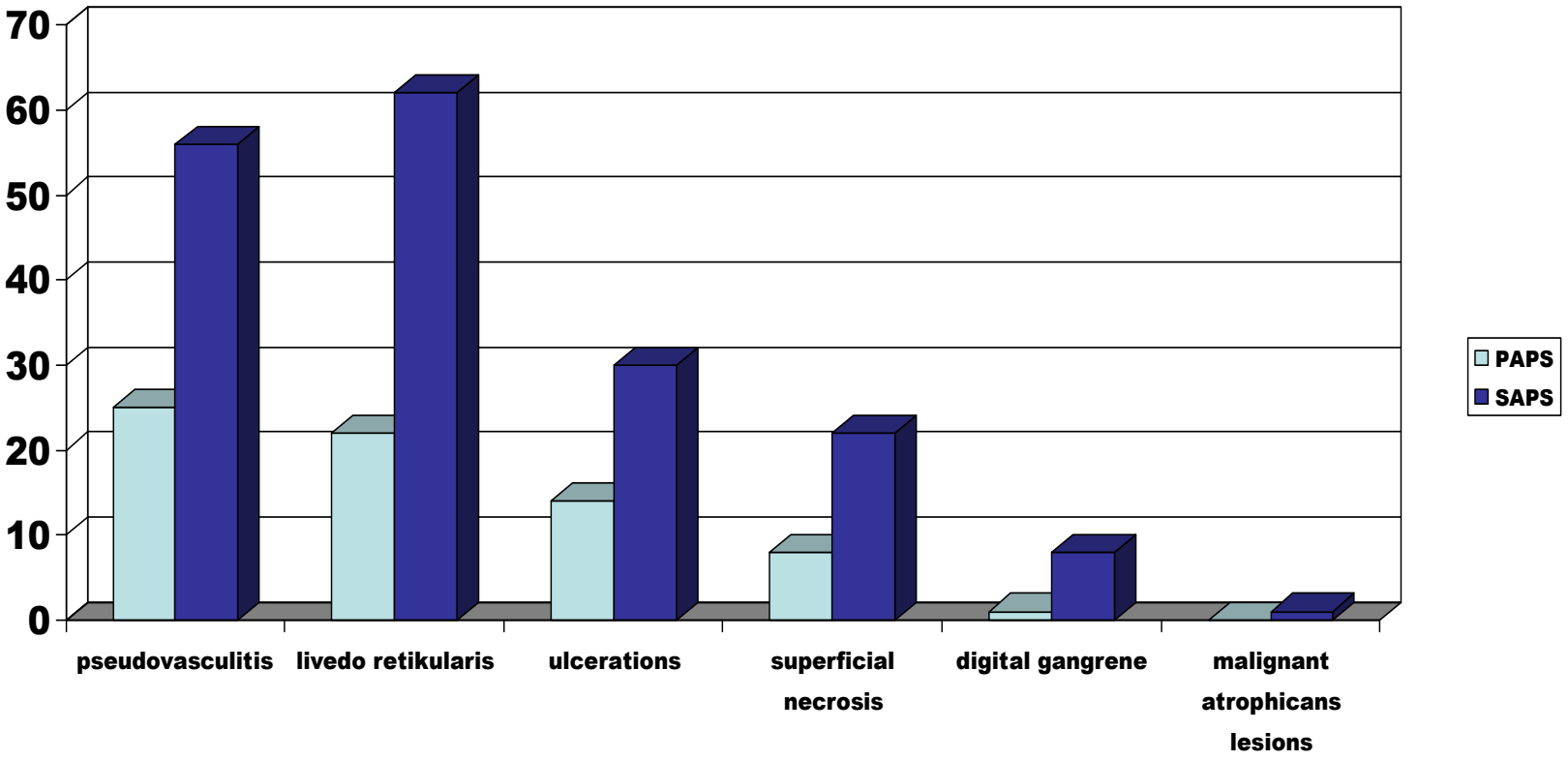
- Livedo reticularis
- Skin ulcerations
- Pseudovasculitis
- Digital Gangrene



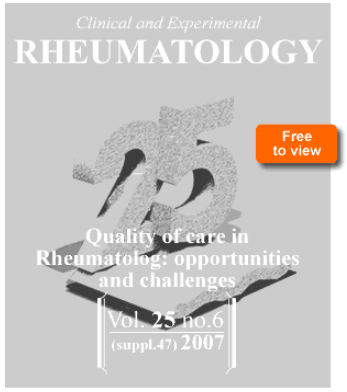




Skin non-thrombotic manifestations



Stojanovich L, MD, PhD

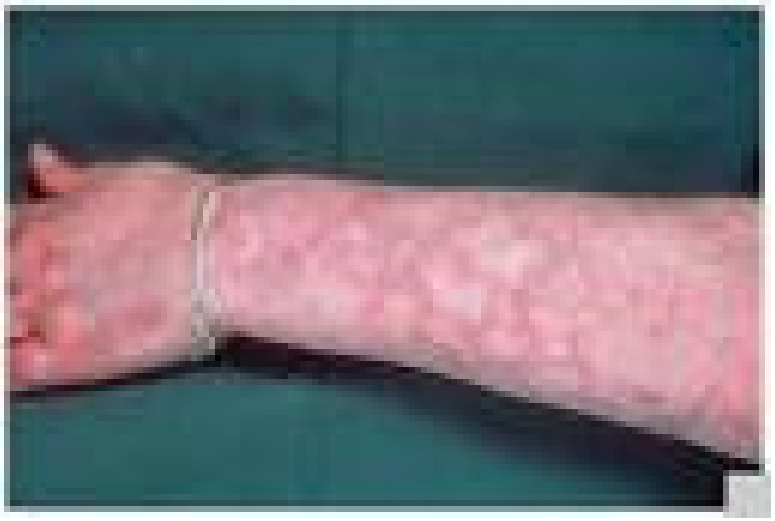


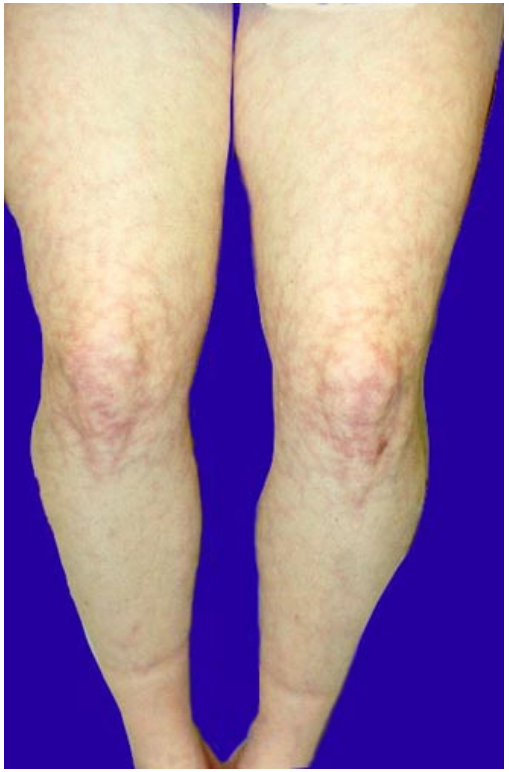
Livedo reticularis is a marker for predicting multi-system thrombosis in antiphospholipid syndrome

E. Toubi[1], I. Krause[2,3], A. Fraser[3], S. Lev[3], L. Stojanovich[4], J. Rovensky[5], M. Blank[2], Y. Shoenfeld[2]

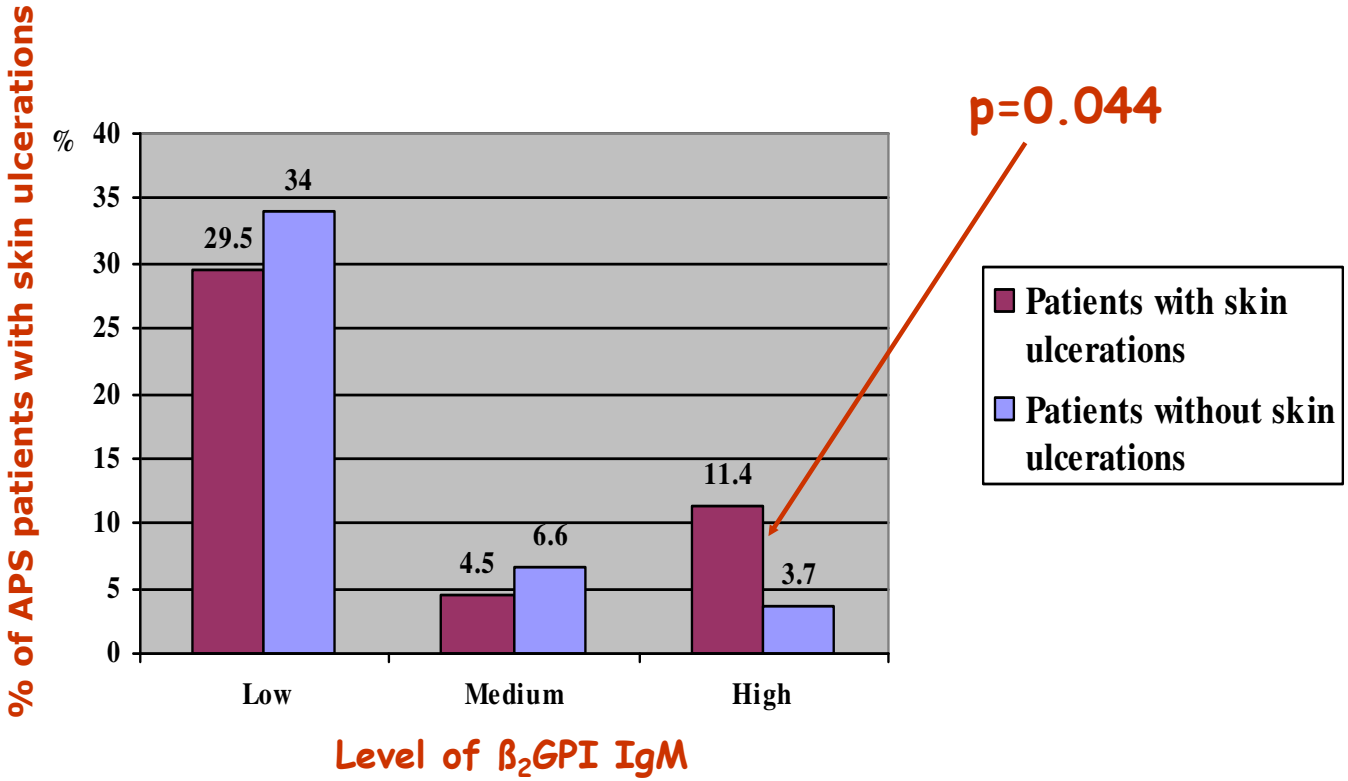
[1]Division of Allergy and Clinical Immunology, Bnai Zion Medical Center, Haifa; [2]Department of Internal Medicine B and Center of Autoimmune Diseases, Sheba Medical Center, Tel Hashomer; [3]Department of Medicine E, Rabin Medical Center, and Sackler Faculty of Medicine, Tel-Aviv University, Israel; [4]Department of Rheumatology and Hospital Center, Bezanijskakosa, Belgrade, Serbia; [5]Research Institute of Rheumatic Diseases, Piestany, Slovakia.

31% pts had Livedo reticularis

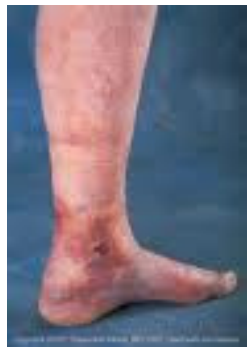




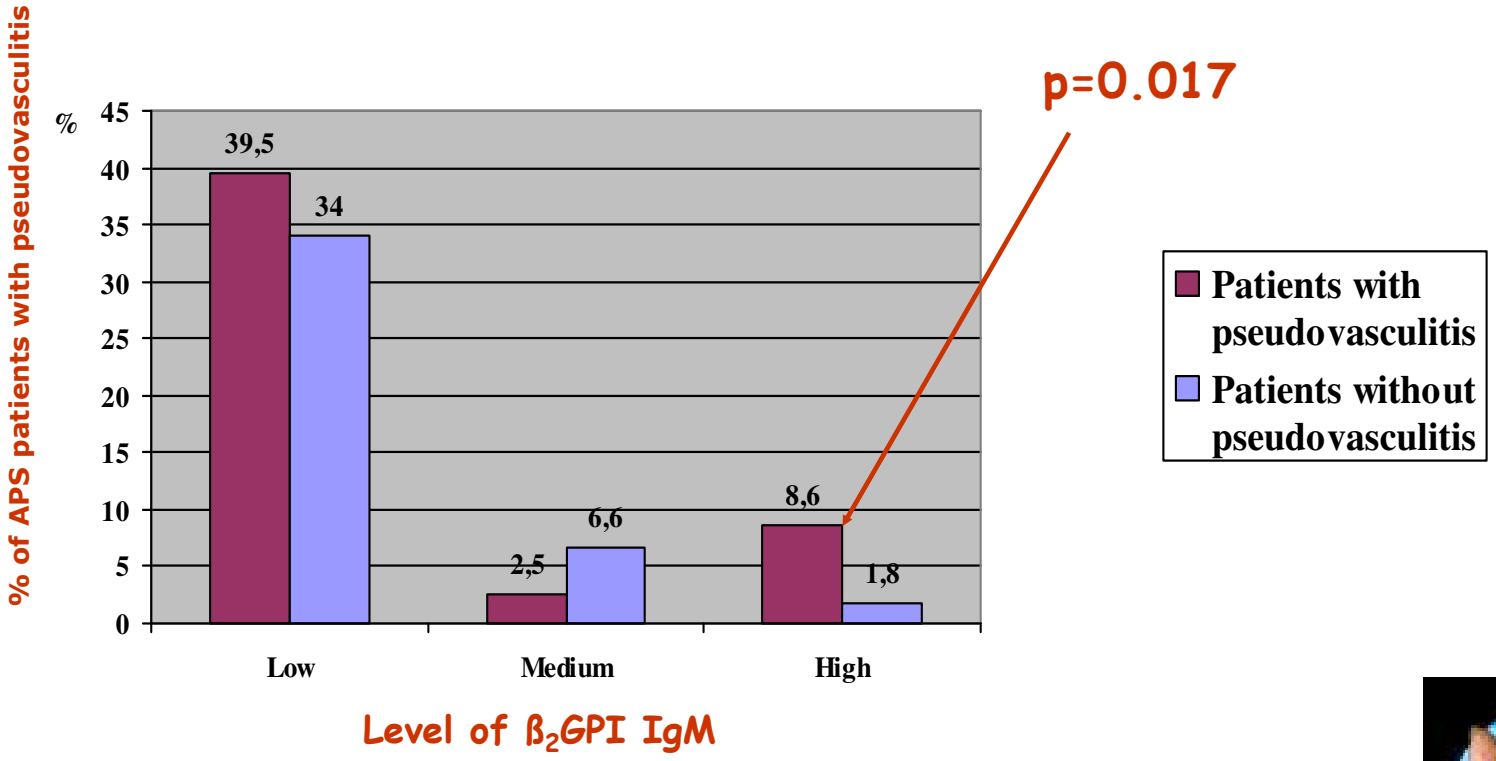
ß$_2$GPI IgM levels in APS with and without skin ulcerations

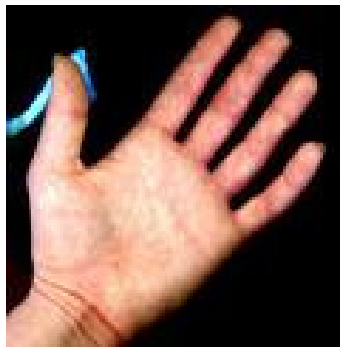


Stojanovich L, MD, PhD



ß$_2$GPI IgM levels in APS with and without pseudovasculitis

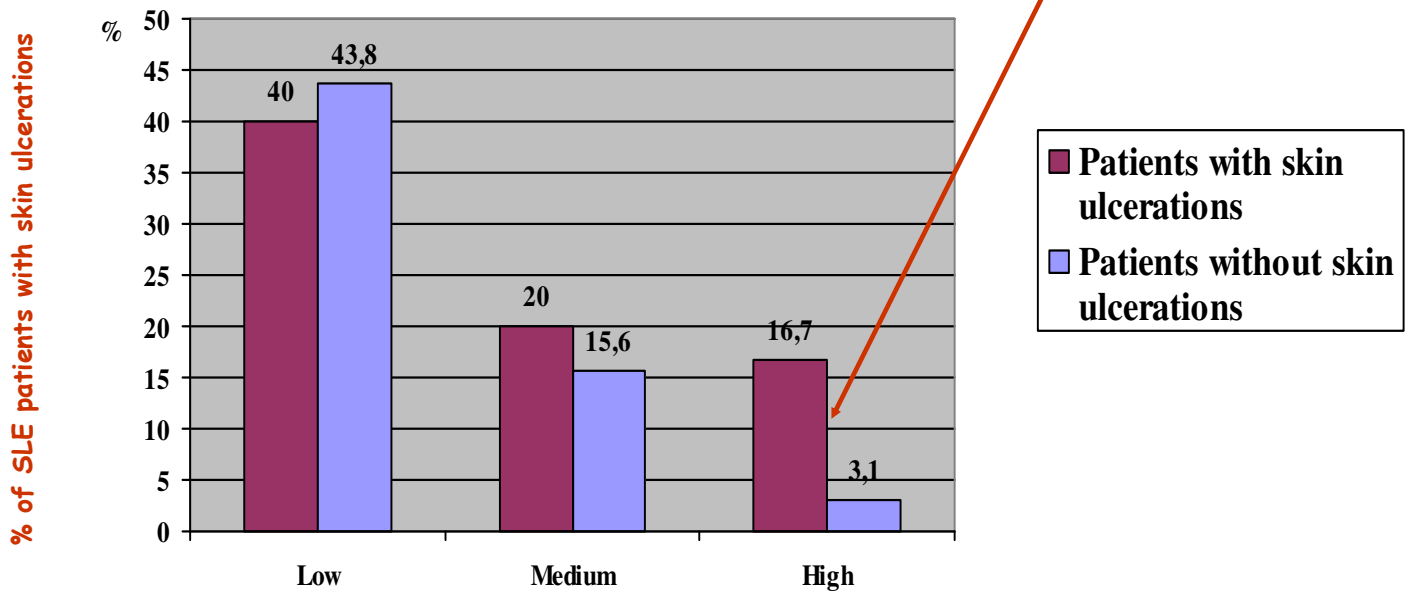




Stojanovich L, MD, PhD

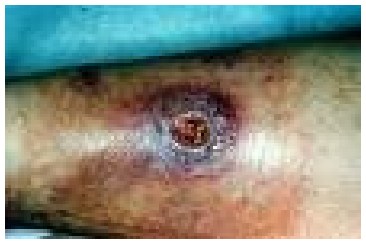
aCL IgM levels in SLE with and without skin ulcerations

p=0.049

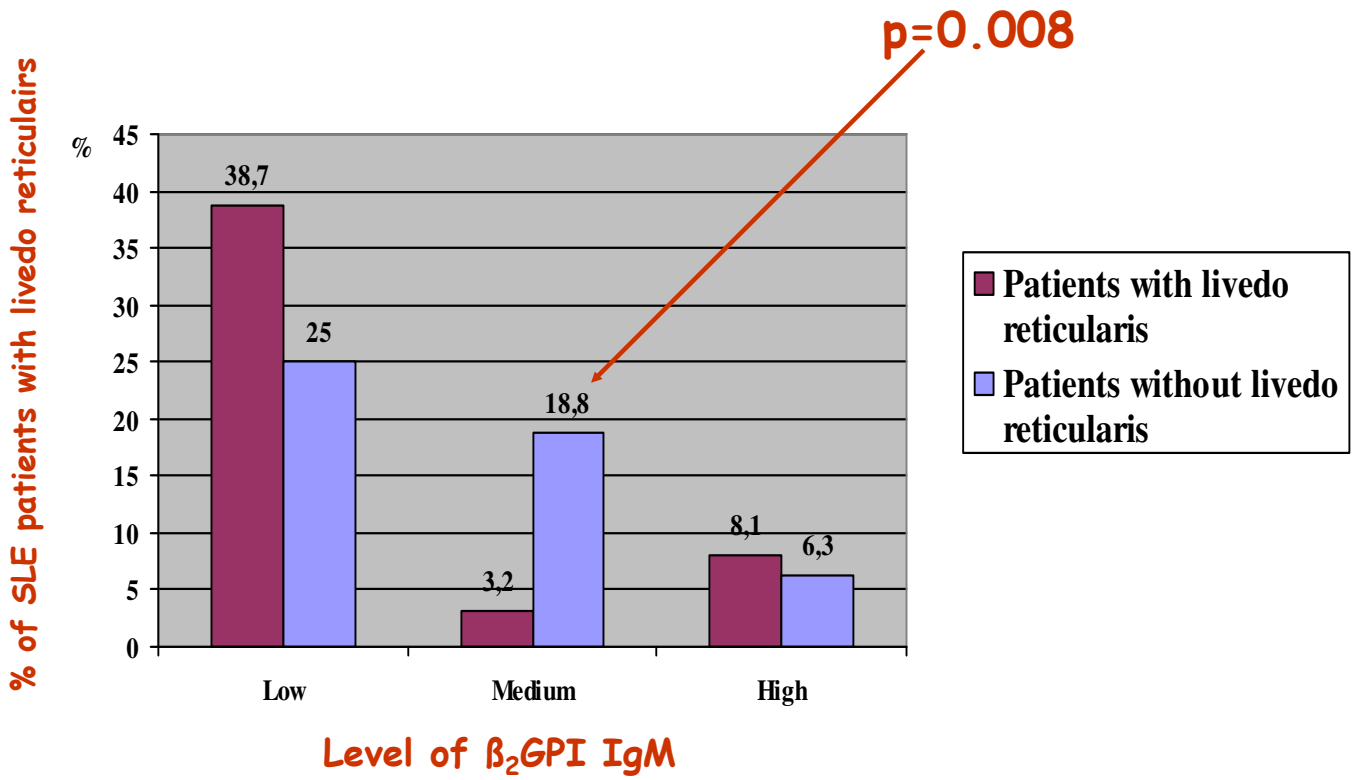


Level of aCL IgM

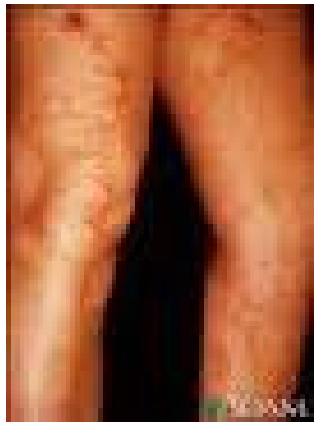
Stojanovich L, MD, PhD



ß$_2$GPI IgM levels in SLE with and without livedo reticularis



Stojanovich L, MD, PhD



Wrapping up

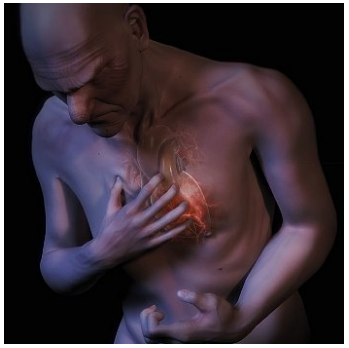
- ✓ Our study results showed correlations between skin lesions and various levels of antiphospholipid antibodies.
- ✓ Patients with Hughes Sy and high levels of ß$_2$GPI IgM are more prone to skin ulcerations and pseudovasculitis.
- ✓ Pseudovasculitis is more common in patients with high levels of aCL IgM.
- ✓ High levels of ß$_2$GPI IgM may play a predictive role in livedo reticularis in SLE patients */from our registry/*.

Results

There was no correlation between non-criteria APS cardiologycal manifestations and:

- ✓ others clinical manifestations of SLE
- ✓ cardiovascular risk factors (including diabetes) **(p> 0.05)**
- ✓ SLE activity (SLEDAI) and other parameters

Results



There was a correlation between:

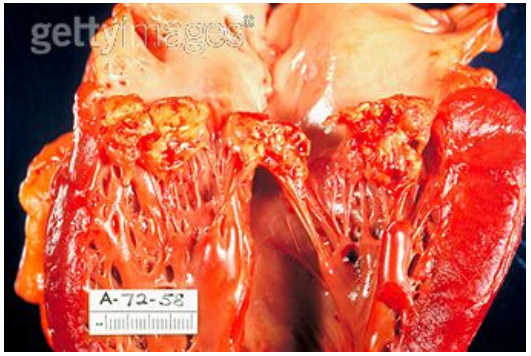
Patients with aCL – IgM and:

- ***CABG/PTCA (p=0.026)***

coronary artery bypass grafting/ percutaneus coronary artery angioplasty

- **Pseudoinfective endocarditis *(p=0.037)***

Results

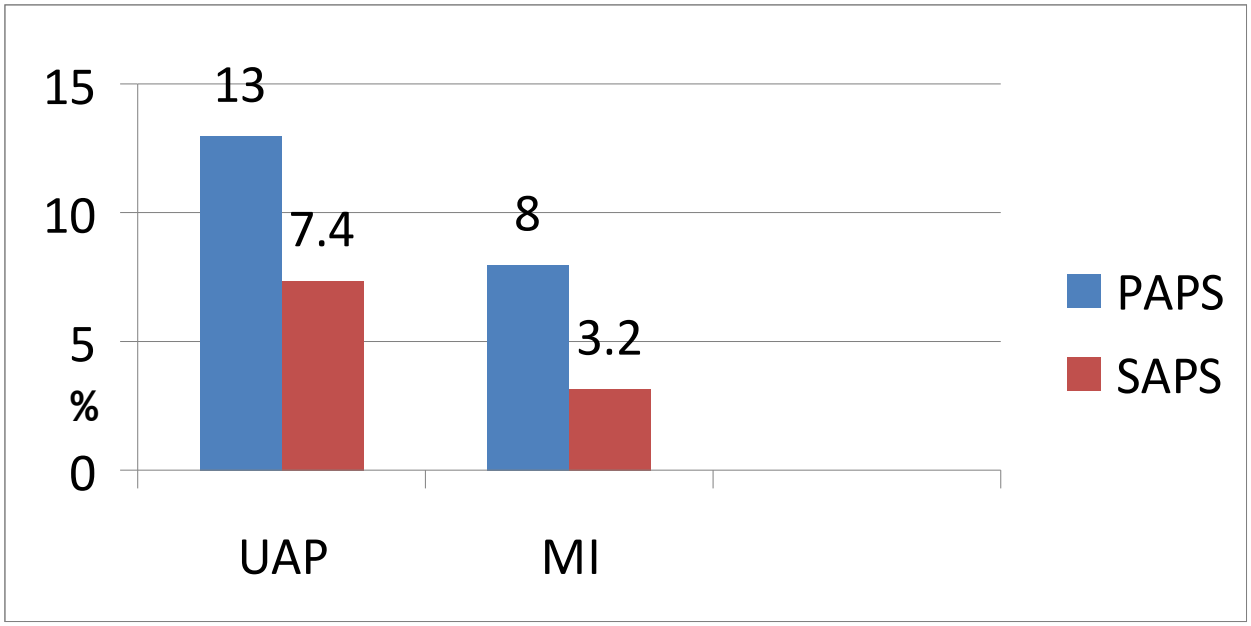


There was a correlation between:

Pseudoinfective endocarditis and:

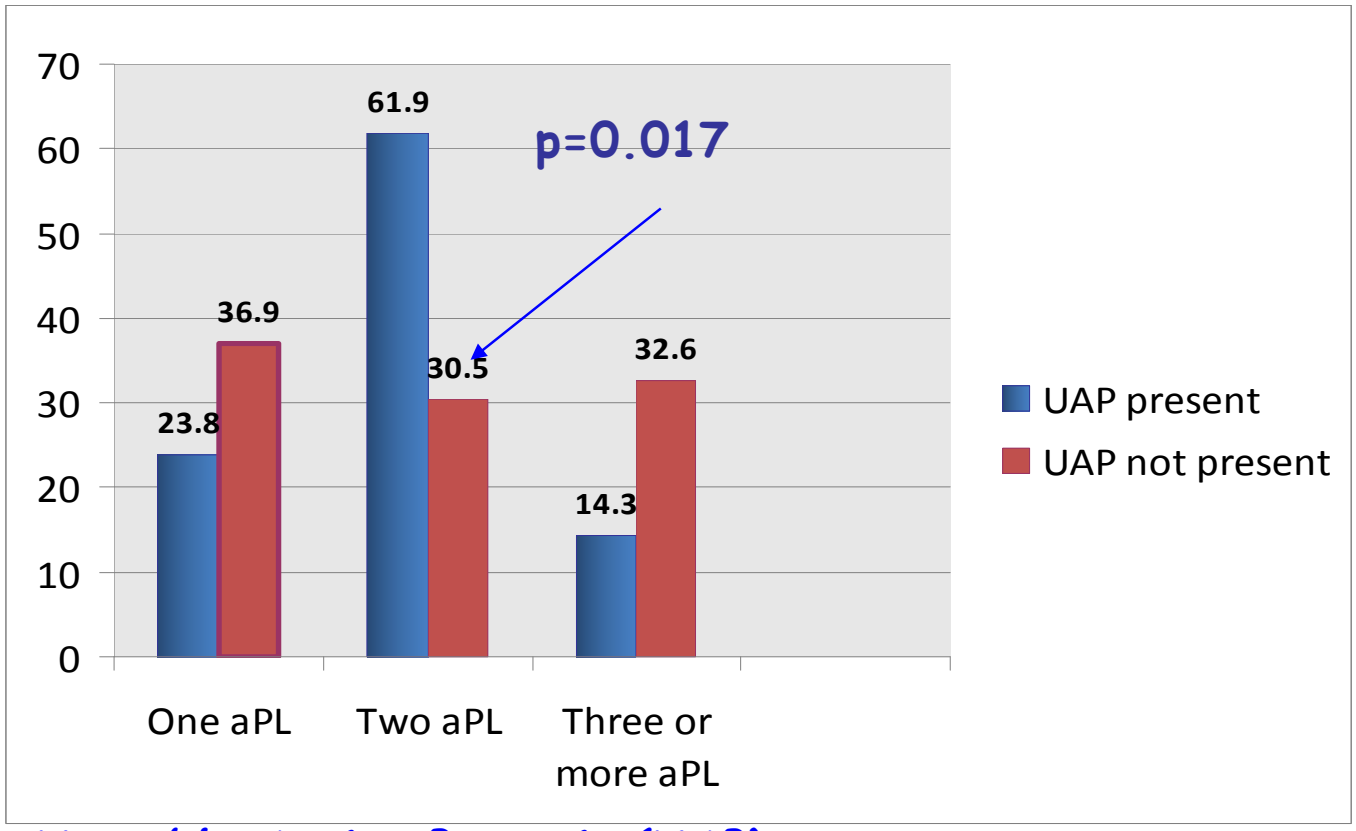
- **Patients with aCL - IgM** ***(p=0.037)***
- **Patients without LA** ***(p=0.014)***

Results



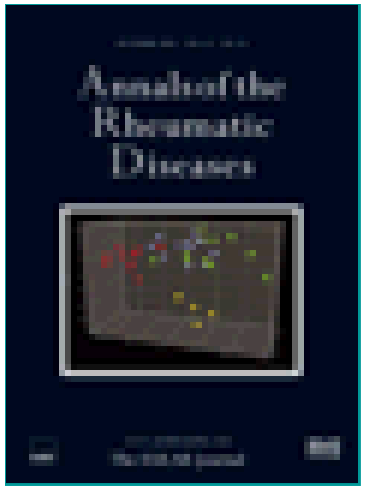
PAPS and SLE patients did not differ among themselves with regard to the occurrence of MI (p = 0,102) and UAP (p = 0.123)
unstable angina pectoris (UAP)

Results



Unstable Angina Pectoris (UAP)

Stojanovich L, MD, PhD



ARD ONLINE

Close Association between valvular heart disease and central nervous system manifestations in the antiphospholipid syndrome

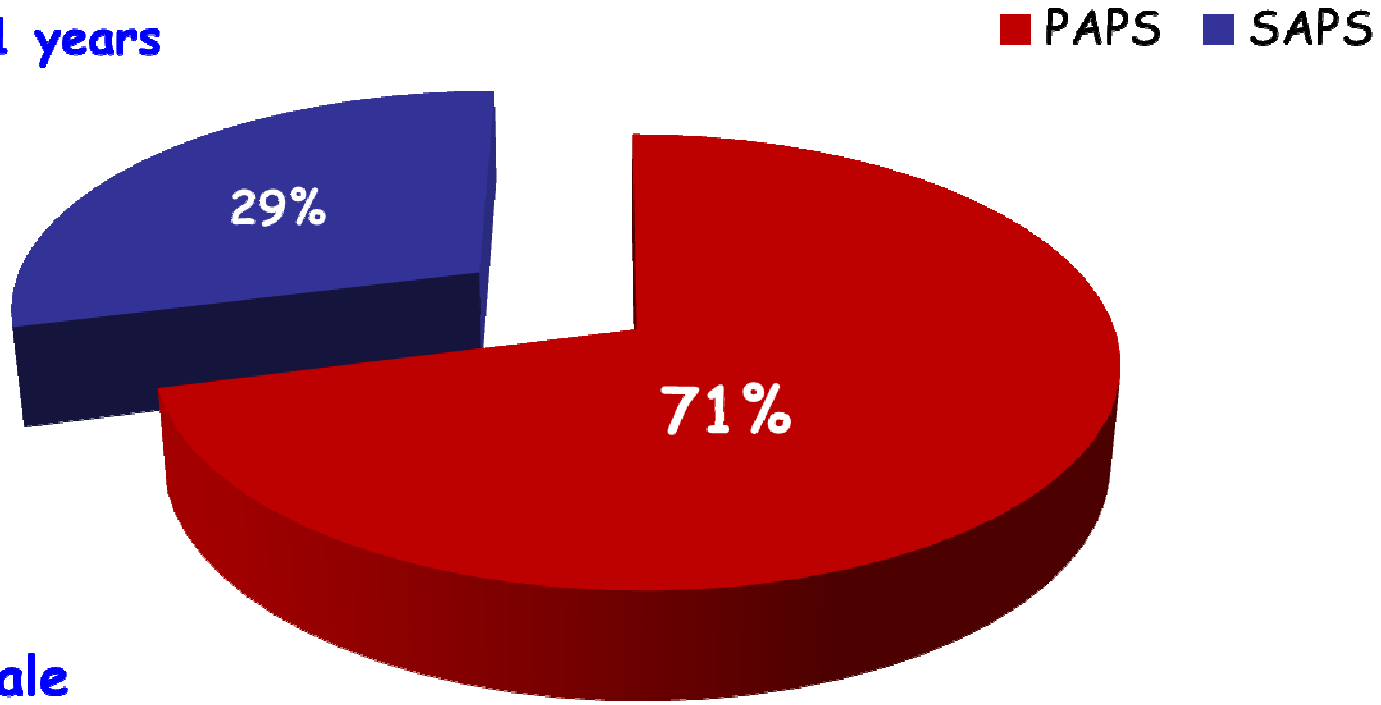
Ilan Krause, Shaul Lev, Abigail Fraser, Miri Blank, Margalit Lorber, Ludmilla Stojanovich, Josef Rovensky, Joab Chapman and Yehuda Shoenfeld

Ann. Rheum. Dis published online 18 Mar 2005;

Stojanovich L, MD, PhD

488 Patients

Average age:
45.03±13.61 years



81.5% female
18.5% male

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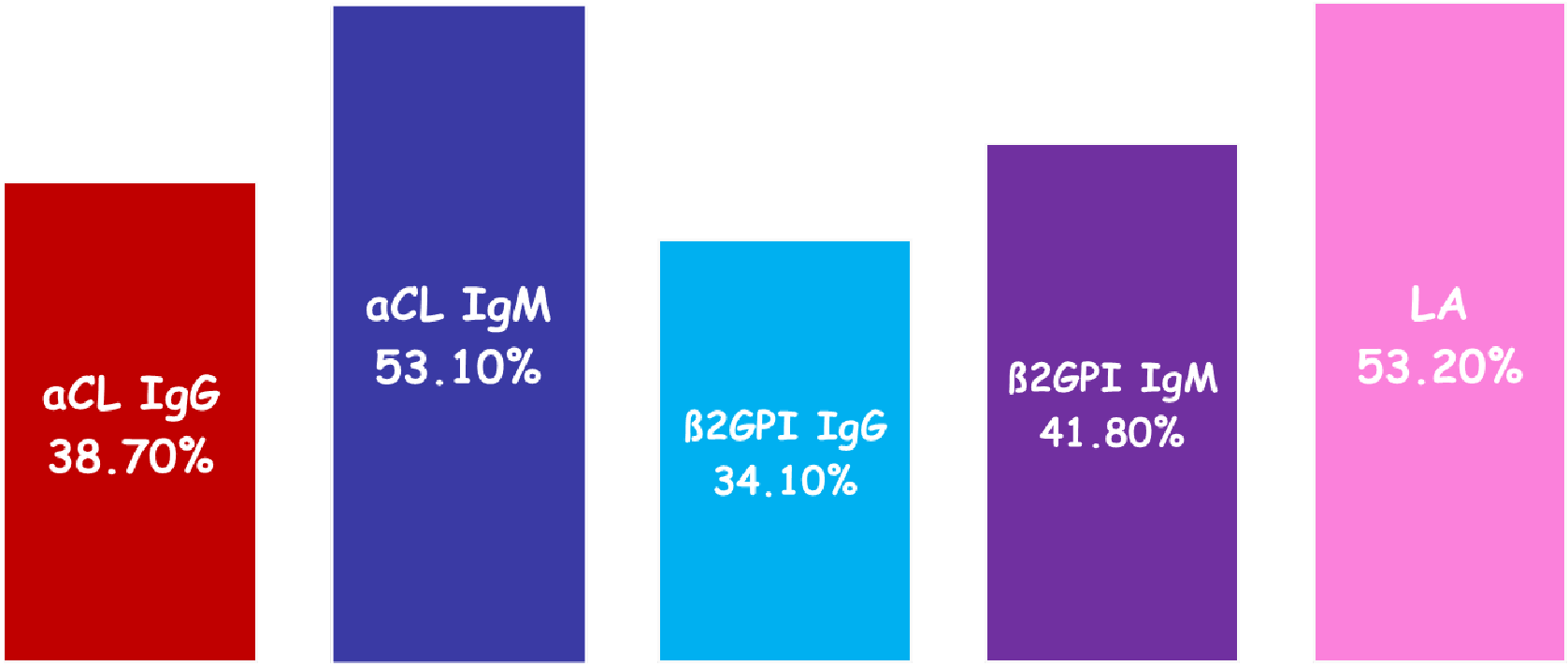
Distribution of aPL



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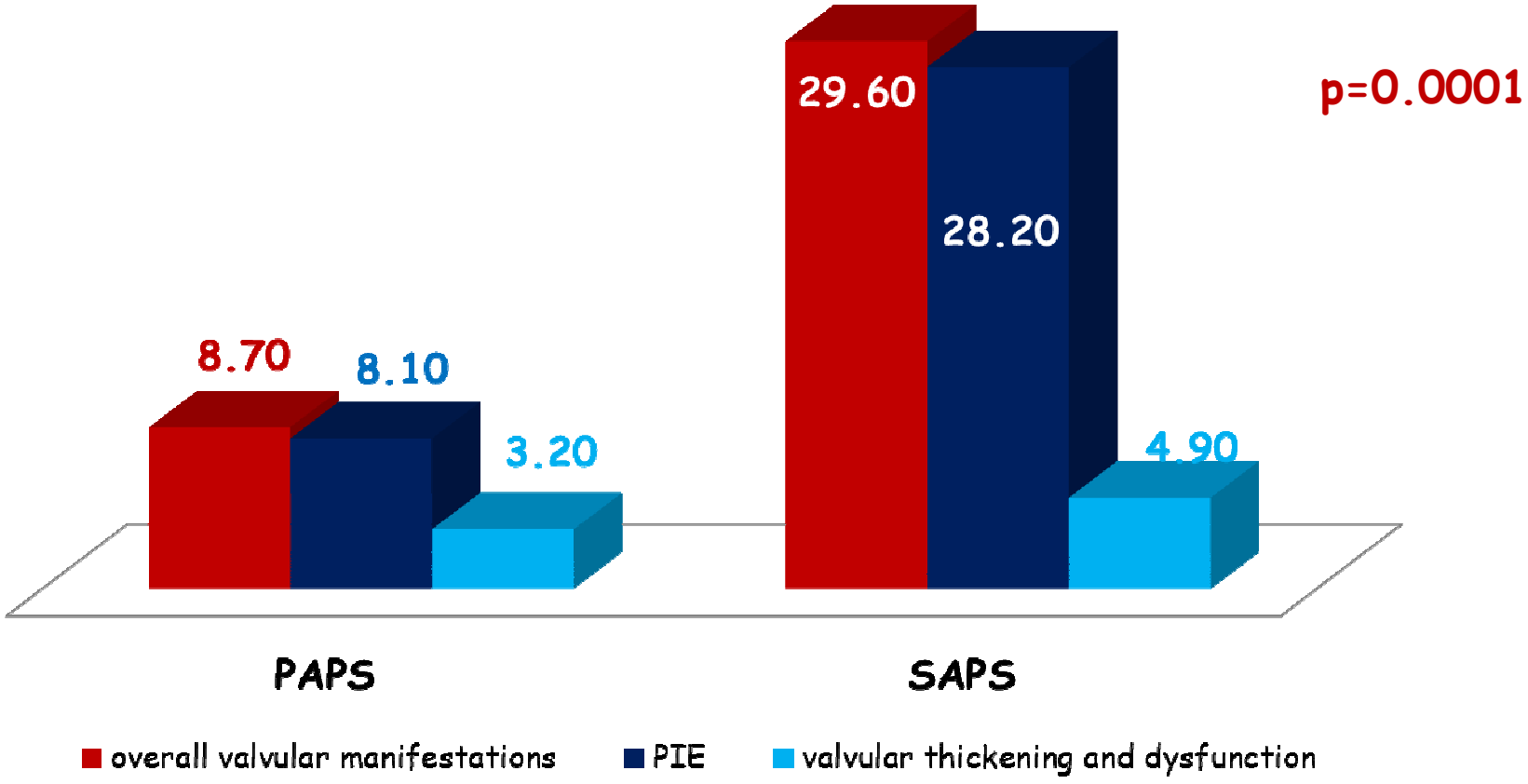
Prevalence of Valvular Manifestations in %



*PIE – pseudoinfective endocarditis

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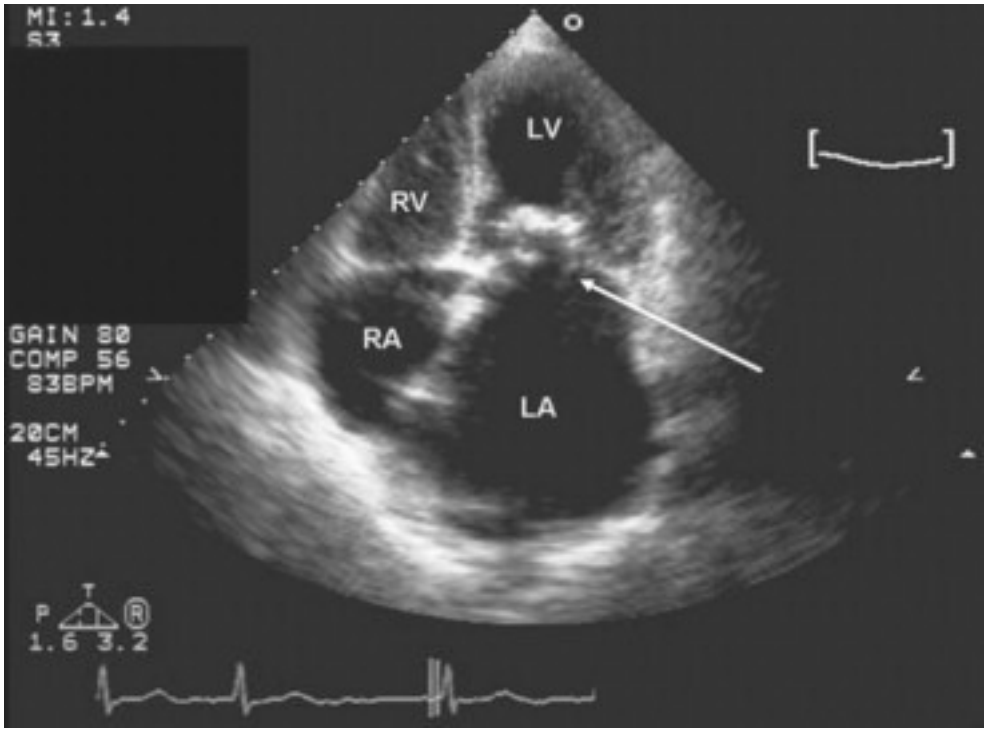
Valvular Vegetations on Mitral Valve in Patient with Antiphospholipid Syndrome



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Valvular Manifestations and aPL Type

aCL IgG	Positive	Negative	p
PIE	19.5%	10.1%	0.004
Valvular dysfunction	6.5%	2.0%	0.013
aCL IgM			
PIE	9.1%	2.6%	0.002

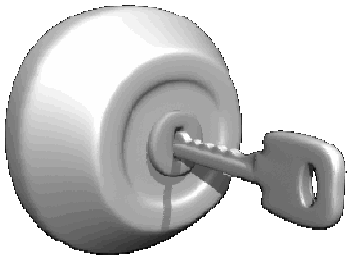
*PIE – pseudoinfective endocarditis

Stojanovich L, MD, PhD

Valvular Manifestations and aPL Titer

- ✓ Valvular manifestations in our cohort were significantly related to titers of aCL antibodies.

- ✓ The level of aCL IgG (p=0.005, Pearson +0.138) were in positive correlation with presence of pseudoinfective endocarditis.



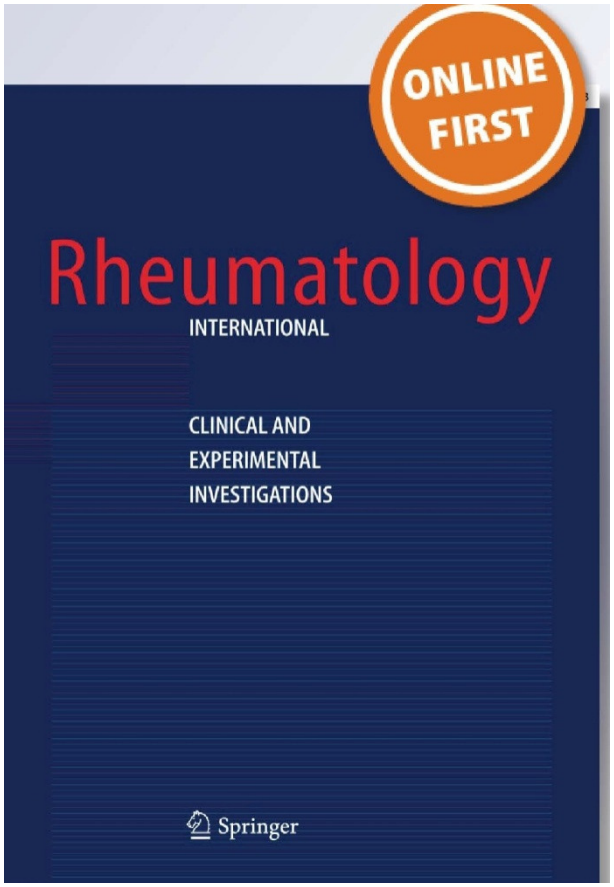
Take-home messages

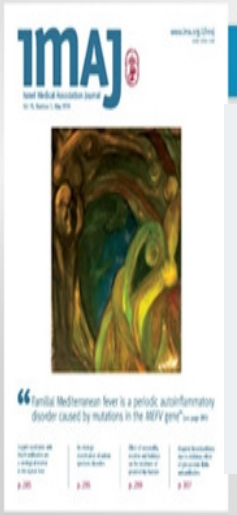
- ✓ The Serbian National APS Registry allowed us to ascertain a significantly increased incidence of endocarditis development in APS patients with aCL-IgM.
- ✓ Presence of LA was significantly connected to lower incidence of pseudoinfective endocarditis.
- ✓ Patients with APS had higher incidence of CABG:*coronary artery bypass grafting.*

Does the presence of secondary antiphospholipid syndrome in patients with systemic lupus erythematodes accelerate carotid arteries intima-media thickness changes?

Aleksandra Djokovic, Lj. Stojanovich, N. Stanisavljevic, V. Bisenic, S. Radovanovic, I. Soldatovic &

Rheumatology International
Clinical and Experimental Investigations





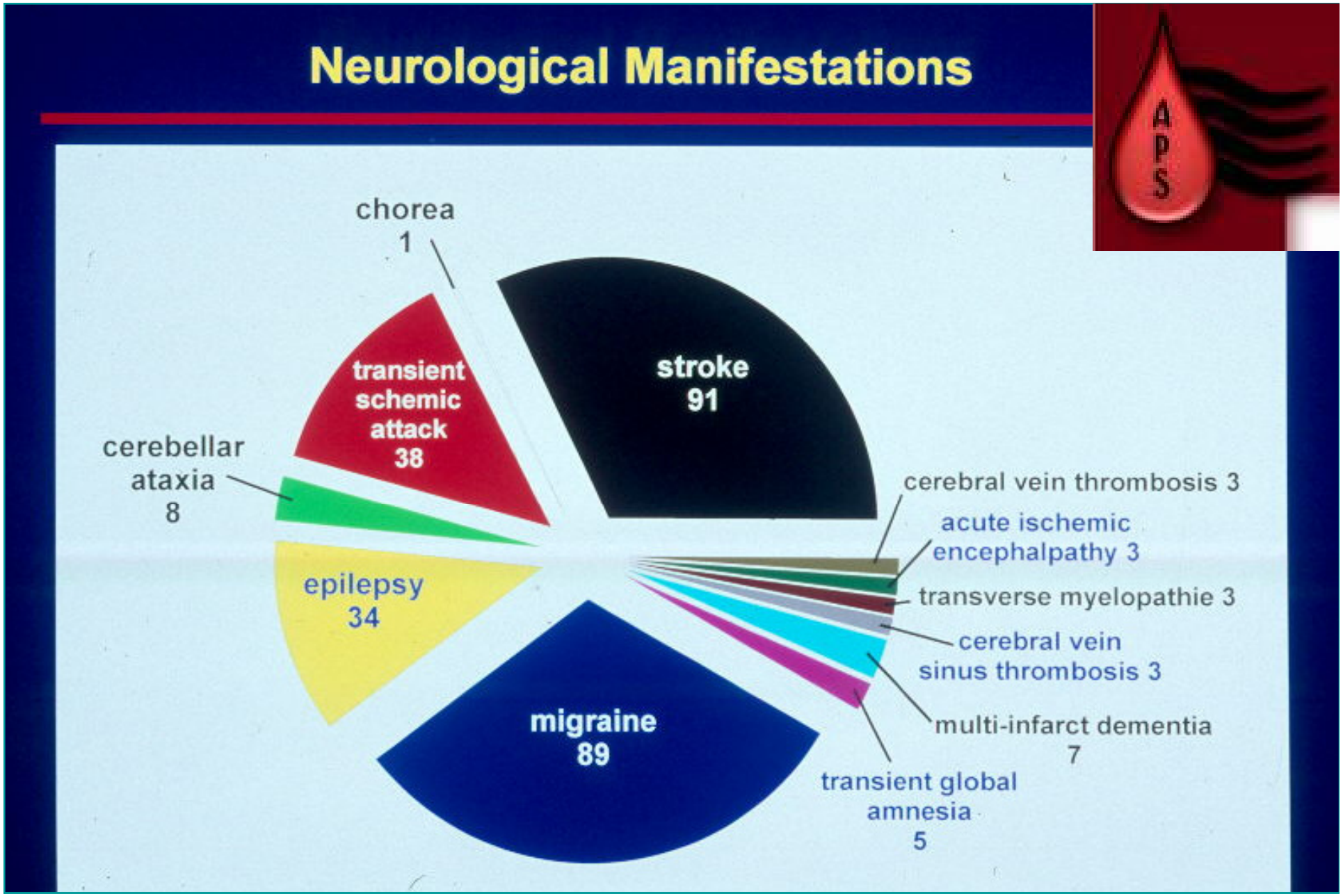
Vol 16, Number 5, May 2014

ORIGINAL ARTICLES

Association between Cardiac Manifestations and Antiphospholipid Antibody Type and Level in a Cohort of Serbian Patients with Primary and Secondary Antiphospholipid Syndrome

Aleksandra Djokovic, Ljudmila Stojanovich, Milica Kontic, Natasa Stanisavljevic, Slavica Radovanovic and Dragomir Marisavljevic

Neurological Manifestations



Stojanovich L, MD, PhD

SCHEDULE

TIMETABLE

May 5th, 2013

08:00-08:30 - Registration
08:30-9:00 - Entrance test

09:00-10:00 - Prof. Hughes GV
Hughes syndrome (the antiphospholipid syndrome): a disease of our time

10:00-11:00 - Prof. Shoenfeld Y
Infections and vaccines in the etiology of antiphospholipid syndrome

11:00-12:00 - Prof. Khamashta MA
Management of antiphospholipid syndrome

12:00-12:30 - Break

12:30-13:30 - Prof. Cervera R
APS: Lessons from the Euro-Phospholipid Project

13:30-14:30 - Prof. Alekberova Z
The problem of APS in the Russian Federation

14:30-15:30 - Prof.Stojanovich L.
Lessons from the Serbian Antiphospholipid Project

May 6th, 2013

09:00-10:00 - dr N.Stanisavljević, mr sc med
The role of endothelial and haematological factors for the development of thrombosis in antiphospholipid syndrome

10:00-11:00 - dr B.Pazin, mr sc med
The role of antiphospholipid antibodies in pregnancy outcomes

11:00-12:00 - dr.A.Djoković, mr sc med
Cardiological manifestations of antiphospholipid syndrome

12:00-12:30 - Break

12:30-13:00 - dr.M.Kontić, dr sc med
Pulmonary manifestations in APS

13:00-13:30 - dr. B. Trninić
Skin manifestations in APS

13:30-14:00 - dr.D.Popović-Kuzmanović,mr sc med
Genetic and immuno-serological markers of APS

14:00-14:30 - Doc J.Šaponjski, dr sc med
New approaches for early diagnosis of occlusive disease in APS

14:30-15:00 - Doc S. Jelić, dr sc med
Metabolic syndrome in APS patients

15:00-16:00 - Exit test and Congress evaluation
16:00 - Certificate distribution

Bezanijska Kosa
University Medical Center
Belgrade University, Serbia

presents

INTERNATIONAL CONGRESS

ANTIPHOSPHOLIPID SYNDROME
(*HUGHES SYNDROME*)

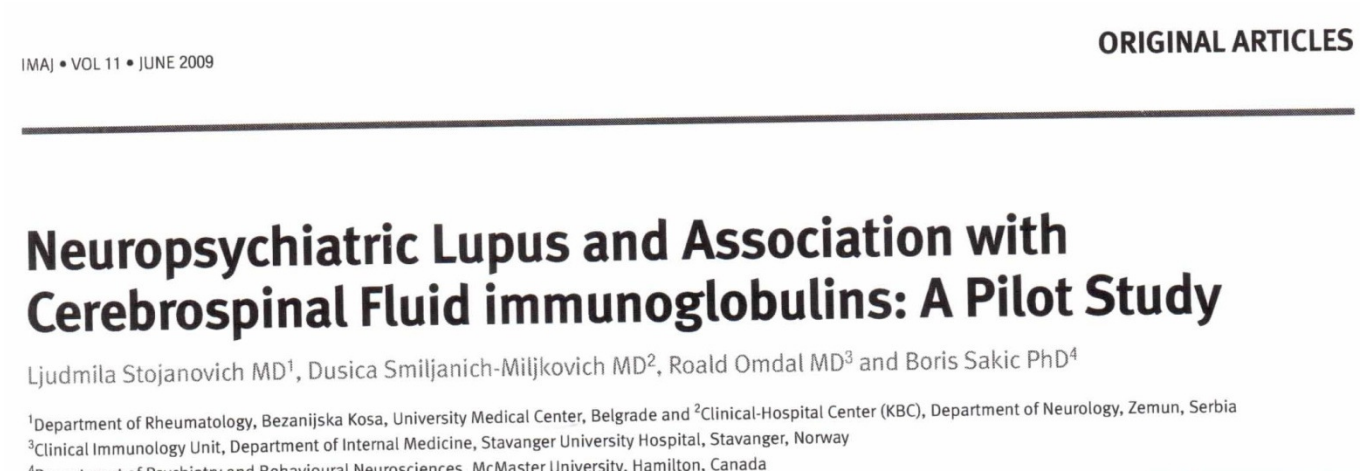
IMPORTANCE OF MULTIDISCIPLINARY APPROACHES

30 YEARS SINCE DEFINITION

AMPHITHEATER
"BEZANIJSKA KOSA" BELGRADE
May 5-6, 2013

METHODOLOGY
electrophysiological tests

- Electroencephalography (EEG)
- Evoked potentials (EP)
- Electromyoneurography (EMNG)



IMAJ • VOL 11 • JUNE 2009 ORIGINAL ARTICLES

Neuropsychiatric Lupus and Association with Cerebrospinal Fluid immunoglobulins: A Pilot Study

Ljudmila Stojanovich MD[1], Dusica Smiljanich-Miljkovich MD[2], Roald Omdal MD[3] and Boris Sakic PhD[4]

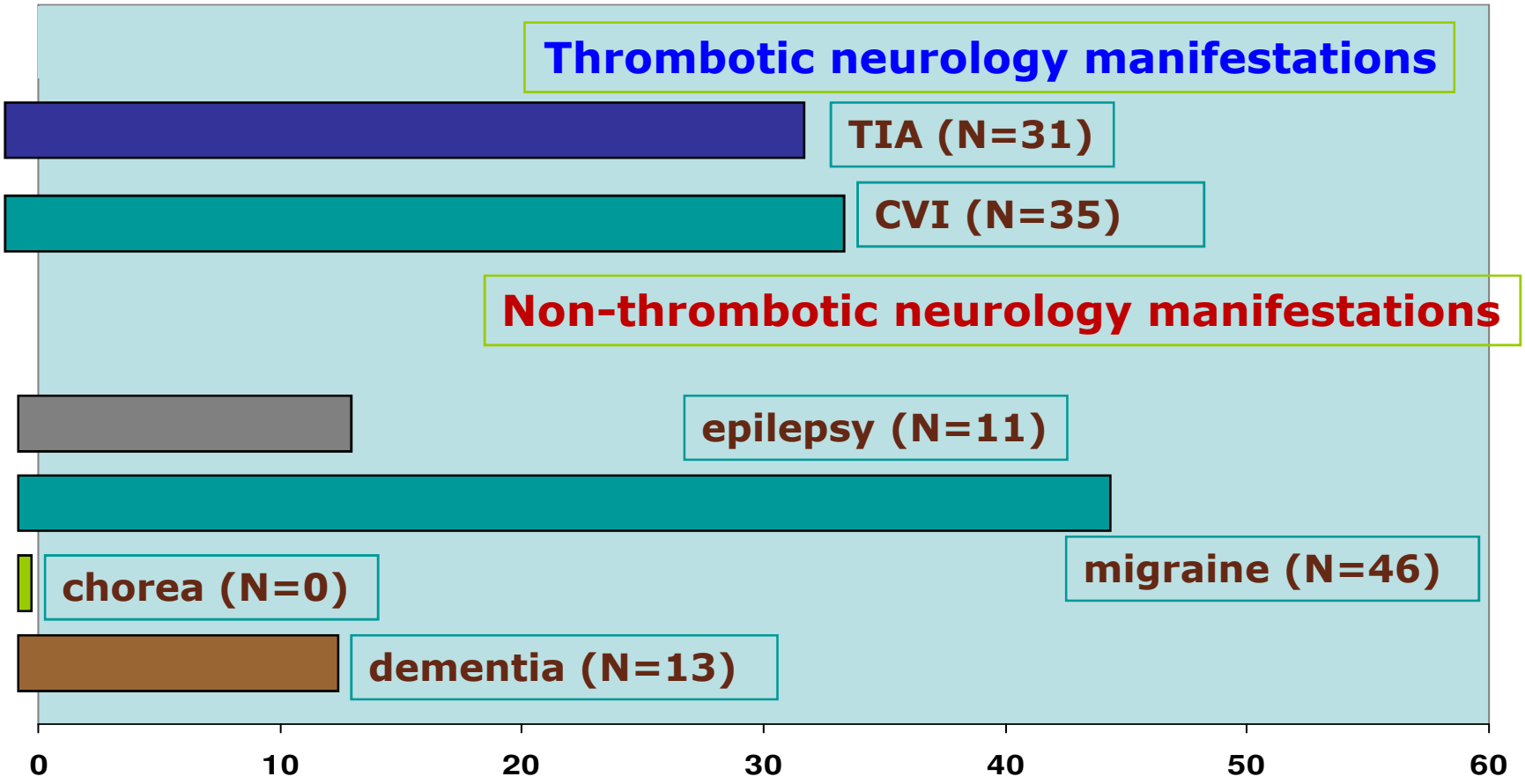
[1]Department of Rheumatology, Bezanijska Kosa, University Medical Center, Belgrade and [2]Clinical-Hospital Center (KBC), Department of Neurology, Zemun, Serbia
[3]Clinical Immunology Unit, Department of Internal Medicine, Stavanger University Hospital, Stavanger, Norway
[4]Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Canada

Stojanovich L, MD, PhD

METHODOLOGY
MRI Findings

Multiple microinfarctions	41.4%
Brain atrophy	18.9%
Large infarction	10.3%
Increased gray matter density	5.3%
More than one abnormal finding	20.7%

Frequency of Neurology Manifestations in PAPS patients



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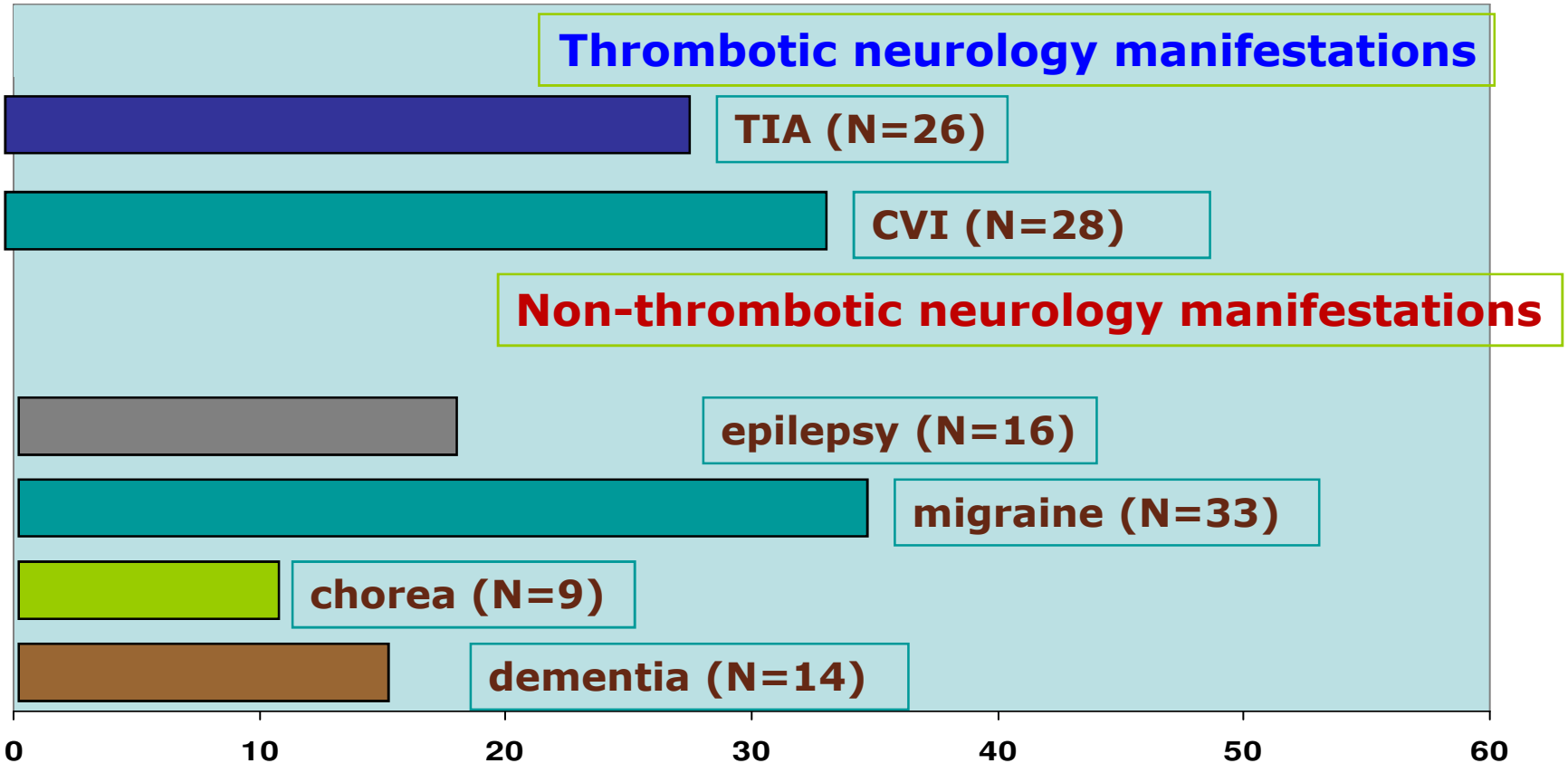
Frequency of Neurology Manifestations in SLE patients



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Comparison of frequency of neurological manifestations between PAPS and SAPS pts

	PAPS	SAPS	p
Transient ischemic attack	21.6%	27%	0.237
Chorea	0%	7.8%	0.000*
Epilepsy	5%	19.1%	0.001*
Migraine	28%	34.8%	0.026*
Transient global amnesia	1.4%	1.7%	0.769
Acute ischemic encehalopathy	1.4%	4.3%	0.305
Anterior spinal artery syndrome	0%	0.9%	0.550
Cehalea	24%	13.9%	0.031*
Vertigo	8.3%	3.5%	0.093
Sy depressivum	3.7%	0%	0.037*

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Results

There was statistically significant correlation between

- epilepsy and high levels of aCL IgG (p=0.021) and IgM (p=0.032)
- dementia and medium levels of ß2GPI IgG (p=0.047)
- TIA and medium levels of aCL IgG (p=0.007)

Results
PAPS

There was statistically significant correlation between:

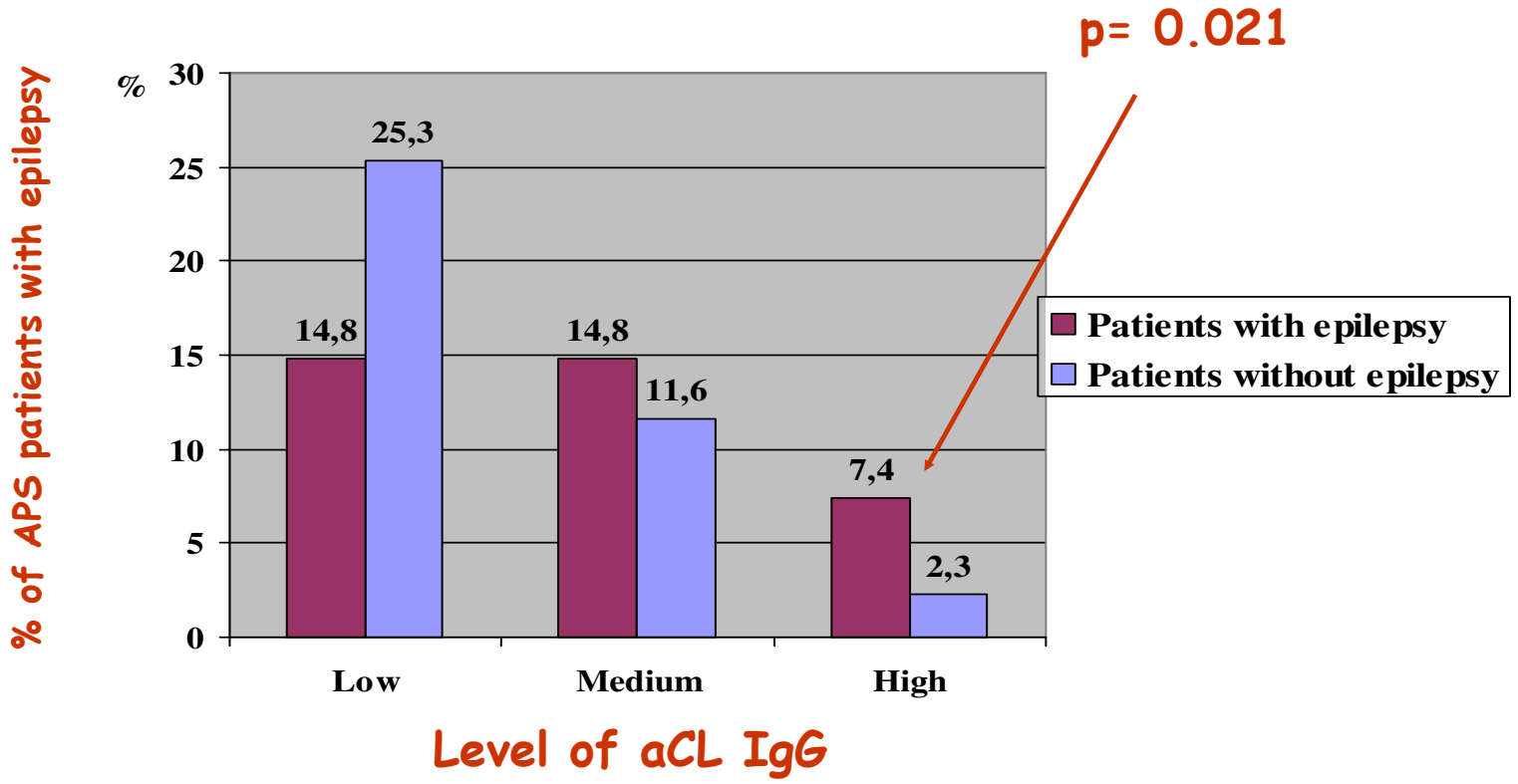
- TIA and high levels of ß2GPI IgM (p=0.0137)
- migraine showed negative correlation with high levels of ß2GPI IgM(p=0.003)

Results
SLE patients

There is statistically significant correlation between chorea and

- medium aCL IgG (p= 0.003)
- ß2GPI IgM titers (p= 0.047)

aCL IgG levels in APS with and without epilepsy



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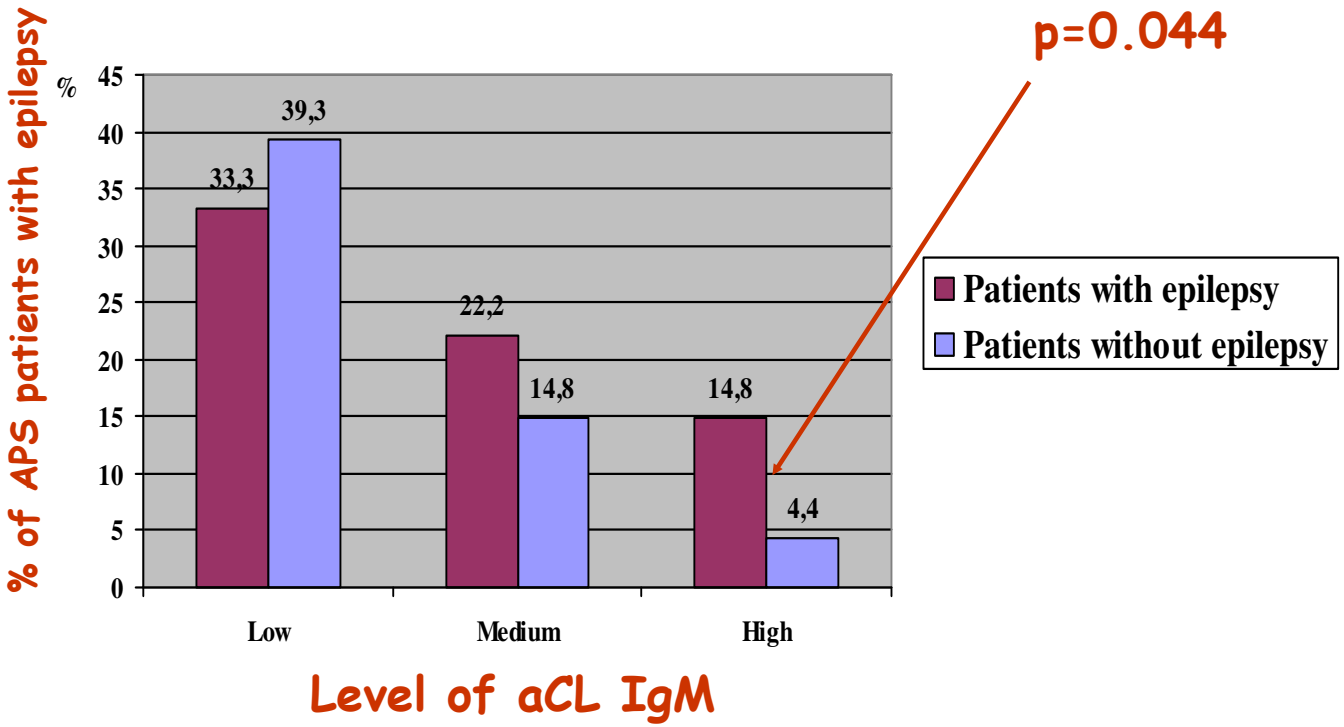
aCL IgM levels in APS with and without epilepsy



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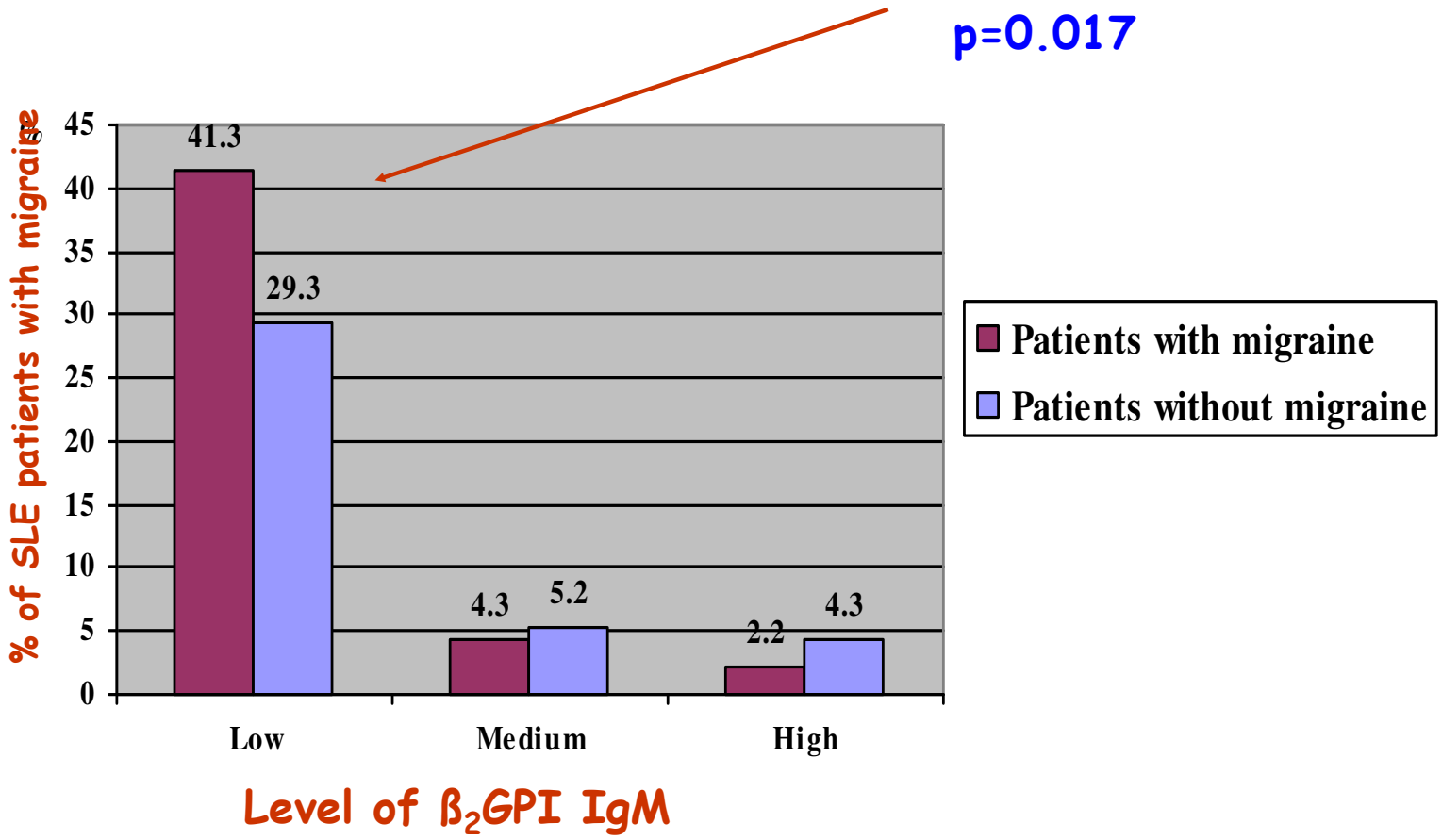
ß$_2$GPI IgM levels in PAPS with and without migraine



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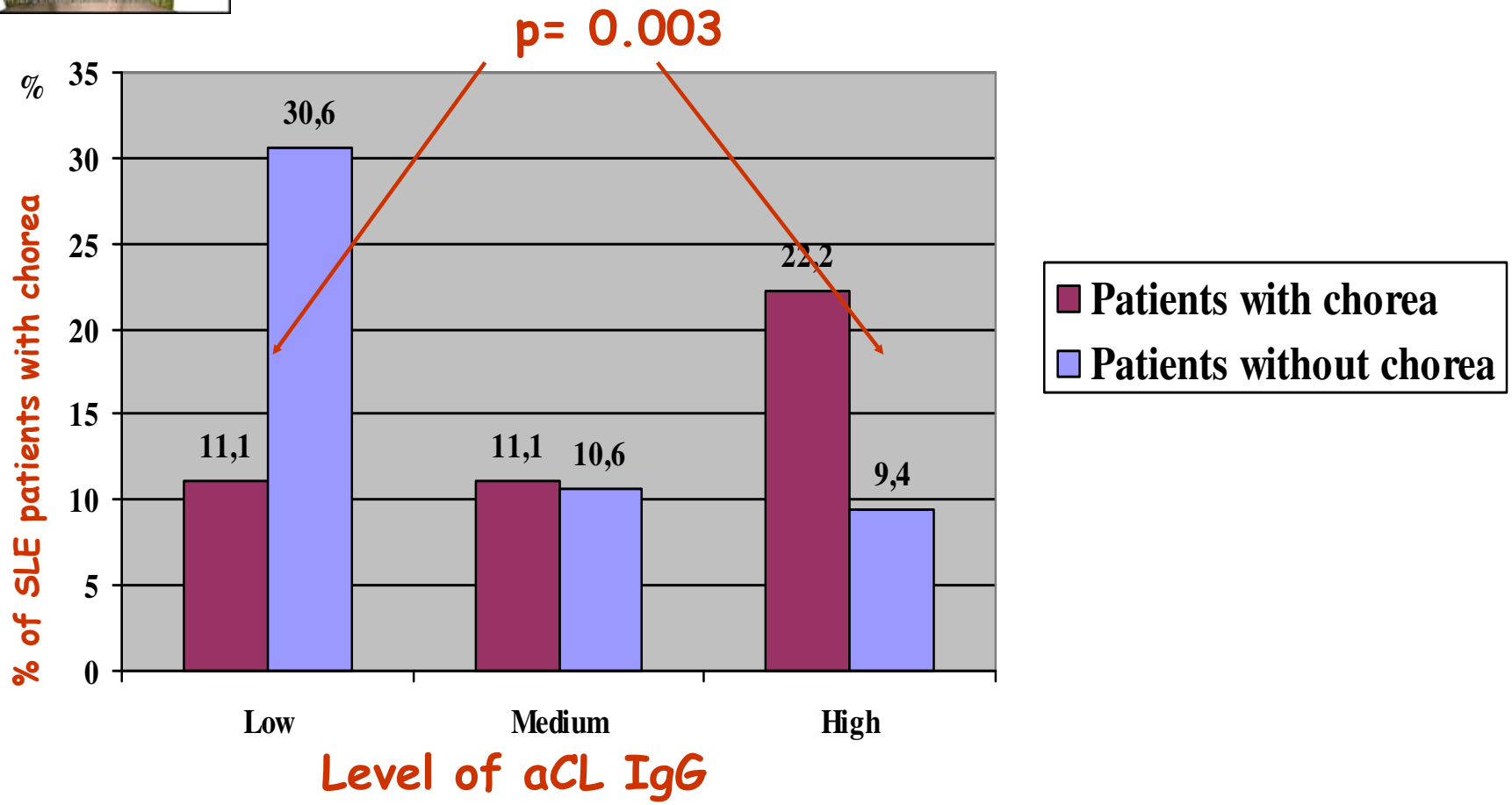
aCL IgG levels in SLE with and without chorea



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Correlation between neurological and cardiac manifestations in PAPS

PAPS patients		Transient ischemic attack			Epilepsy			Transient global amnesia			Depression		
		-	+	p	-	+	p	-	+	p	-	+	p
Non stable angina pectoris	-	158	36	0.002*	187	7	0.006*	193	1	0.002*	187	6	0.217
	+	13	11		20	4		22	2		22	2	
Valve vegetations	-	160	40	0.064	193	7	0.001*	198	2	0.285	15	3	0.002*
	+	11	7		14	4		17	1		194	5	

Association between non-thrombotic neurological and cardiac manifestations in patients with antiphospholipid syndrome

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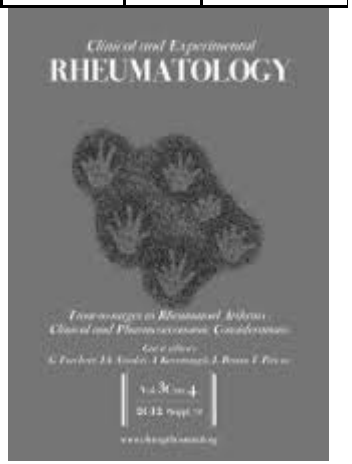
[4]Rheumatology Clinic, Institute Niska Banja, Medical Faculty, University of Nis;
[5]Faculty of Medicine, University of Belgrade, Belgrade, Serbia.



Correlation between neurological and cardiac manifestations in SAPS

SAPS patients		Transient ischemic attack			Acute ischemic encephalopathy			Vertigo		
		not present	present	p	not present	present	p	not present	present	P
Non stable angina pectoris	not present	80	24	0.004 *	102	2	0.000*	101	3	0.285
	present	4	7		8	3		10	1	

International Conference on Cardiology (Cardiology'11) (part of Summer WORLDMED)

Prague, Czech Republic, September 26-28, 2011

Plenary Lecture 3:

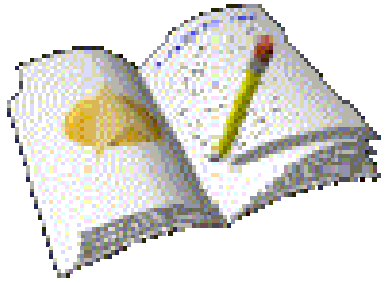
Non-Thrombotic Neurological and Cardiac Manifestations in Antiphospholipid Syndrome

by **Prof. Ljudmila Stojanovich**, Belgrade University, SERBIA.

Take-home messages

- ✓ APS patients can be presented with a wide variety of nontrombotic manifestations.
- ✓ The certain aPL type and level correlated with non-criteria APS manifestations, suggesting their predictive or protective role.
- ✓ Our study confirmed that presence of cardiac manifestations may be a risk factor for several types of CNS involvement in APS.

Take-home messages



- ✓ The number of aPL do not play a role in non-criteria APS manifestations.
- ✓ Not only high, but also medium and low levels of aPL, correlate with the onset of non-criteria APS manifestations, including cardiological, neurological, and dermatological.

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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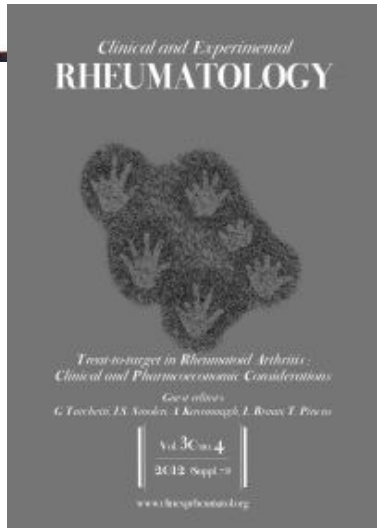

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