Relationship between cerebrovascular and valvular manifestations in a Serbian cohort of patients with antiphospholipid syndrome

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Abstract

Objective

Antiphospholipid syndrome (APS) may manifest itself as a primary (PAPS) or secondary disease, most commonly in the context of systemic lupus erythematosus (SLE) with various neurological and cardiac manifestations in its occurrence. The objective of this study was to investigate the relationship between cerebrovascular (stroke and transient ischaemic attack (TIA)) and valvular manifestations in a Serbian cohort of APS patients.

Methods

This is cross sectional study of 508 APS patients: 360 PAPS and 148 APS patients associated with SLE (SAPS). aPL analysis included detection of anticardiolipin antibodies (aCL: IgG/IgM), anti-ß2glycoprotein I (ß2GPI: IgG/IgM), and LA.

Results

The prevalence of valvular manifestations (valvular vegetations and valvular thickening and dysfunction not related to age) in our cohort was significantly higher in SAPS group. (28.4% vs. 8.6%, p=0.0001). Age was strong predictor for stroke and TIA occurrence in both groups as well as gender (stroke more likely occurred in male SAPS and TIA in male PAPS patients). Presence of ß2GPI IgG in SAPS patients was significantly related to stroke (p=0.018), whereas ß2GPI IgG negative PAPS patients were more prone to TIA. Valvular manifestations were significantly related to TIA in both groups of patients and were independent risk factors for TIA in PAPS (OR 3.790 CI 1.597-8.998 p=0.003).

Conclusion

In this cross-section analysis of a large cohort of Serbian APS patients, there was a strong relationship between valvular and cerebrovascular manifestations, suggesting a more cautious approach regarding neurological symptoms, especially in PAPS patients with valvular vegetations present.

Key words

antiphospholipid syndrome, valvular manifestations, stroke, national cohort study

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Introduction

Antiphospholipid syndrome (APS) or Hughes syndrome represents a systemic autoimmune disorder characterised by arterial and/or venous thrombosis, multiple and recurrent foetal losses, often accompanied by a thrombocytopenia and elevated levels of antiphospholipid antibodies (aPL), such as lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and anti- β_2GPI antibodies (1-3). This syndrome is considered primary (PAPS) if unassociated with any other connective tissue disease or secondary (SAPS) if it appears in association with other autoimmune disorders, mainly systemic lupus erythematosus (SLE) (4-13).

Neurological manifestations in APS are common, including stroke, transient ischaemic attack (TIA), epilepsy, dementia, cognitive deficits, headaches, behavioural abnormalities, psychiatric disorders, seizures, chorea, multiple sclerosis-like, myelopathy, transverse myelitis and ocular symptoms, and may be associated with this syndrome in both the primary and secondary forms (4). Many of these manifestations are interrelated and may occur simultaneously in the same patient. Neurological disorders may result from vascular thrombotic events or without thrombotic events – by direct injury to neuronal tissue (7). This spectrum of neurological disorders in patients with antiphospholipid antibodies is sometimes referred as the "neuropsychiatric APS". The objective of this cross-sectional study was to observe and investigate associations between cerebrovascular and valvular manifestations in a large cohort of Serbian APS patients. Differences between patients with PAPS and SAPS were also analysed.

Materials and methods

Our study includes a total of 508 APS patients; 360 were PAPS patients (283 female and 77 male, mean age 44.0±12.9), while 148 had APS associated with SLE (133 female and 15 male, mean age 47.7±14.8). Patients were consecutively included from the year 2000 in University Hospital Center Bezanijska Kosa. All patients met the 2006 revised Sydney criteria for APS (14). The diagnosis of APS was made by the presence of aPL and other diagnostic criteria (by Doppler ultrasound, computed tomography, heart ultrasound or other for arterial and/or venous thrombosis, and multiple and recurrent foetal losses). All patients diagnosed with SLE met the American College of Rheumatology (ACR) classification criteria (15). Disease activity was assessed at the time of enrolment in the study using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score (16) and all included patients were with stable disease. All APS patients were treated with antithrombotic therapy (low-dose aspirin) combined with anticoagulant therapy (warfarin) if thrombotic events have been confirmed and hydroxychloroquine. Patients with secondary APS associated with SLE were on the low dose glucocorticoids (average dose 7.5mg/day).

Clinical data and medication were retrieved from the clinical database and patient records. The presence of comorbidities, such as arterial systemic hypertension (blood pressure ≥140 × 90mmHg or use of anti-hypertensive drugs) and diabetes (glycated haemoglobin 7% or use of medication) as data on smoking habit (any person who smokes every day, occasional smoke and quit smoking less than a year ago) and drugs used, were also evaluated. Among these patients, 14 were presented with catastrophic APS (CAPS), and were included into the international registry of catastrophic APS patients (CAPS Registry), created in 2000 by the European Forum on Antiphospholipid Antibodies (17).

Diagnosis of cerebrovascular and valvular manifestations

Diagnosis of cerebrovascular manifestations was established by clinical findings of transient or permanent focal neurological signs (such as hemiparesis, hemihypesthesia, speech disorder, diplopia, of defects of the field of vision), presence of behavioural changes, migraine headache, seizures, movement disorders, signs of encephalopathy, cognitive decline, or dementia and confirmed by brain magnetic resonance imaging.

Transthoracic echocardiography was performed using a standardised protocol that included M-mode, 2-dimensional (2-D), and Doppler recordings. Valvular lesions were classified to valvular thickness and/or dysfunction (without presence of vegetations) and valvular vegetations, defined as precipitation of thrombus, not containing bacteria, on the valve cusps. The modified Duke criteria utilising pathologic and clinical criteria were used to differentiate between true infective endocarditis and Libman-Sacks endocarditis (18). Transesophageal echocardiographic (TEE) study has been performed in all patients with vegetations in order to confirm the diagnosis and establish the severity of disease.

This study was performed in accordance with the ethical standards of the institutional and national research committee (research grant 175041 for 2011–2014, and TR 32040 for 2011–2017, issued by the Ministry of Science of the Republic of Serbia) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Laboratory tests

All patients were evaluated for the presence aPL, accompanied by routine biochemistry and complete blood cell counts. LA was based on the use of two different screening tests: diluted activated partial thromboplastin time and sensitive activated partial thromboplastin time according to ISHT recommendations (19). LA tests were not performed while the patients were receiving anticoagulant therapy. aCL: IgG/IgM and aβ_2GPI: IgG/IgM antibodies were measured by an enzyme-linked immunosorbent assay (ELISA, Binding Site) and expressed in GPL or phospholipids (MPL) units (GPL-U and MPL-U). Additionally, we followed revised laboratory criteria for APS on two or more occasions at least 12 weeks apart (20, 21). Antinuclear antibodies (ANA) were determined by indirect immunofluorescence on mouse liver and HEp-2 cell substrate. Anti-double-stranded DNA (anti-dsDNA) antibodies were determined by ELISA, Binding Site.

Table I. Distribution of aPL, ANA and anti-dsDNA in the patients with primary and secondary APS.

	PAPS n=360 n (%)	SAPS n=148 n (%)	*p*-value
aCL IgG	107 (29.7)	83 (56.1)	**0.0001****
aCL IgM	172 (47.8)	89 (60.1)	**0.014***
β_2GPI IgG	109 (30.3)	60 (40.5)	**0.038***
β_2GPI IgM	147 (40.8)	67 (45.3)	0.489
LA	198 (55.0)	79 (53.4)	0.769
ANA	45 (12.6)	129 (87.2)	**0.0001****
Anti-dsDNA	3 (0.8)	52 (35.1)	**0.0001****

aPL: antiphospholipid antibodies; ANA: antinuclear antibodies; anti-dsDNA: anti-double-stranded DNA; PAPS: primary antiphospholipid syndrome; SAPS: secondary antiphospholipid syndrome; aCL: anticardiolipin antibodies; β_2GPI: anti- β_2 glycoprotein 1 antibodies; LA: lupus anticoagulant.
*statistically significant; **highly statistically significant.

Table II. Comparison of frequency of cerebrovascular and valvular manifestations between patients with primary and secondary APS.

	PAPS/ n=360 n (%)	SAPS/ n=148 n (%)	*p*-value
TIA	68 (18.9)	42 (28.4)	**0.024***
Stroke	80 (22.2)	43 (29.1)	0.111
Valvular changes overall	31 (8.6)	42 (28.4)	**0.0001****
Valvular vegetations	28 (7.8)	40 (27.0)	**0.0001****
Valvular thickening and dysfunction	11 (3.1)	7 (4.7)	0.428

TIA: Transient ischaemic attack; PAPS: primary antiphospholipid syndrome; SAPS: secondary antiphospholipid syndrome.
*statistically significant, **highly statistically significant.

Statistics

Results are presented as mean ± standard deviation or count (percent) depending on data type. Groups were compared using student's *t*-test, Mann-Whitney U-test, Pearson chi-square test or Fisher's exact test, depending on data type and distribution (for continuous data). Multivariate logistic regression was used to explore the association between a dependent variable and independent predictors. All data were analysed using SPSS 20.0 (IBM corp.) statistical software. All *p*-values less than 0.05 were considered significant.

Results

Prevalence of aPL and cerebrovascular and valvular manifestations and their relationship in PAPS and SAPS group

Distribution of aPL as well as ANA and anti-dsDNA antibodies in PAPS and SAPS groups is presented in Table I. Patients with SAPS had significantly higher prevalence of aCL IgG, aCL IgM and β_2GPI IgG antibody positivity. Next step in our study was to compare frequency of stroke and TIA and certain valvular mainfestations (valvular thickening and dysfunction, vegetations and overall) between patients with PAPS and SAPS. As presented in Table II, TIA occurred significantly more often among SAPS patients. Vavular manifestations in the means of valvular vegetations occurred more often in SAPS patients and the difference was highly statistically significant.

Valvular changes overall as well as valvular vegetations occurred more significantly in male PAPS patients (p=0.021, p=0.032, respectively). Age was significant risk factor for neurological and valvular manifestations occurrence in both groups of patients (PAPS and SAPS).

Furthermore, the association between presence of aPL type and certain neurological and valvular manifestations was analysed. β_2GPI IgG negative PAPS patients had higher prevalence of TIA (22.7% *vs*. 10.1%, p=0.05). Conversely, presence of β_2GPI IgG was significantly related to stroke in SAPS patients (p=0.018). There was signifi-

Table III. Relationship between stroke and TIA and valvular manifestations in PAPS and SAPS group.

PAPS	TIA n (%)				Stroke n (%)			
	Not present	Present	*p*-value	OR (CI 95%)	Not present	Present	*p*-value	OR (CI 95%)
Valvular manifestations overall	16 (5.5)	15 (22.1)	**0.0001****	4.882 (2.276-10.473)	20 (7.1)	11 (13.8)	0.072	2.072 (0.948-4.531)
Valvular thickening and dysfunction	7 (2.4)	4 (5.9)	0.134	2.545 (0.723-8.953)	7 (2.5)	4 (5.0)	0.271	2.053 (0.585-7.197)
Valvular vegetations	14 (4.8)	14 (20.6)	**0.0001****	5.148 (2.322-11.413)	18 (6.4)	10 (12.5)	0.095	2.079 (0.919-4.706)
SAPS								
Valvular manifestations overall	25 (23.6)	17 (40.5)	**0.045***	2.203 (1.028-4.721)	29 (27.6)	13 (30.2)	0.841	1.136 (0.521-2.474)
Valvular thickening and dysfunction	4 (3.8)	3 (7.1)	0.405	1.962 (0.420-9.166)	3 (2.9)	4 (9.3)	0.194	3.487 (0.746-16.295)
Valvular vegetations	23 (21.7)	17 (40.5)	**0.025***	2.454 (1.136-5.300)	28 (26.7)	12 (27.9)	1.000	1.065 (0.481-2.365)

PAPS: primary antiphospholipid syndrome; SAPS: secondary antiphospholipid syndrome; n: number of patients.
*statistically significant, **highly statistically significant.

Table IV. Binary regression analysis for TIA and stroke occurrence in PAPS and SAPS patients.

	TIA						Stroke					
	PAPS			SAPS			PAPS			SAPS		
	OR	95% CI	*p*-value	OR	95%CI	*p*-value	OR	95% CI	*p*-value	OR	95%CI	*p*-value
Age	1.074	1.047-1.102	**0.0001****	1.046	1.013-1.079	**0.005****	1.081	1.055-1.107	**0.0001****	1.031	1.001-1.061	**0.046***
Gender	1.672	0.856-3.267	0.132	0.911	0.244-3.395	0.421	1.184	0.613-2.284	0.615	3.661	1.087-11.992	**0.036****
Smoking habit	1.801	0.982-3.303	**0.072**	1.611	0.683-3.798	0.625	2.061	1.169-3.636	**0.012***	0.474	0.198-1.136	0.094
Hyperlipidaemia	1.153	0.512-2.601	0.713	1.426	0.552-3.683	0.463	0.439	0.215-1.206	0.065	1.708	0.669-4.364	0.263
Hypertension	0.617	0.174-2.192	0.966	3.939	1.168-13.290	**0.027***	1.731	0.642-6.476	0.352	1.391	0.423-4.573	0.587
ß2GPI IgG	0.271	0.123-0.595	**0.001****	0.870	0.373-2.028	0.746	0.535	0.282-1.012	**0.055**	2.096	0.951-4.622	**0.067**
Valvular manifestations	3.790	1.597-8.998	**0.003****	2.116	0.898-4.985	**0.086**	1.288	0.540-3.076	0.568	0.720	0.302-1.721	0.460

TIA: transient ischaemic attack; PAPS: primary antiphospholipid syndrome; SAPS: secondary antiphospholipid syndrome; ß2GPI: anti- ß2 glycoprotein 1 antibodies. *statistically significant difference; **highly statistically significant difference.

cant relationship between β_2GPI IgM and valvular vegetations in SAPS group (p=0.045).

Relationship between arterial and venous thromboses and cerebrovascular and valvular manifestations in PAPS and SAPS group

PAPS patients with thromboses had significantly higher prevalence of cerebrovascular events. TIA occurred more often in patients with arterial (89.7% *vs*. 28.1%, p=0.0001) and venous thromboses (36.8% *vs*. 22.9%, p=0.021) whereas stroke was significantly related to arterial (87.5% *vs*. 26.1%, p=0.0001) but not to venous thromboses. 80.6% of PAPS patients with valvular manifestations experienced arterial and/or venous thrombosis (p=0.002). Valvular vegetations were related to arterial thromboses (62.1% *vs*. 37.8%, p=0.016) while 90.9% patients with valve thickening and dysfunction had arterial and/or venous thrombosis in the course of main disease (p=0.014).

In the SAPS group TIA as well as stroke was significantly related to arterial (95.2% *vs*. 34.9%, p=0.001, 93.0% *vs*. 35.2%, p=0.0001, respectively), not to venous thromboses. Valvular manifestations appeared more often in patients with arterial and/or venous thromboses (74.4% *vs*. 53.3%, p=0.026), namely related to arterial (65.1% *vs*. 46.7%, p=0.048). Valve thickening and dysfunction occurred more often in SAPS patients with venous thromboses (57.1% *vs*. 17.7%, p=0.028), valve vegetations in patients with arterial thromboses (65.9% *vs*. 46.7%, p=0.044).

Possible impact of anticoagulant regimen was also evaluated. No significant relationship to cerebrovascular manifestations was confirmed (in PAPS group for TIA and stroke p=0.183, p=1.000, respectively, in SAPS group for TIA and stroke p=1.000, p=0.724, respectively)

Predictors of cerebrovascular events in PAPS and SAPS group

We analysed the relationship between stroke and TIA and valvular changes in both, PAPS and SAPS group (Table III). Valvular manifestations overall and valvular vegetations were significantly related to TIA (not to stroke) occurrence in both groups of patients.

Among standard atherosclerotic risk factors (hypertension, smoking habit, hyperlipidaemia, diabetes) smoking habit was significantly related to stroke and TIA in PAPS group (p=0.006, p=0.027, respectively) as well as valve thickening and dysfunction (p=0.028). In SAPS group hypertension was significant risk factor for TIA (p=0.0001), TIA and stroke were significantly re-

lated to hyperlipidaemia presence (p=0.002, p=0.027, respectively). Regarding gender, stroke occurred more significantly in male SAPS patients (p=0.013) and TIA in male PAPS patients (p=0.021).

As presented in Table IV, after adjustment for age, gender, β_2GPI IgG positivity, hypertension, hyperlipidaemia (variables included in model revealed p-values of 0.05 and bellow in univariate analyses), valvular manifestations overall were independent risk factors for TIA in PAPS (OR 3.790 CI 1.597–8.998 p=0.003).

Discussion

In this study we have identified significant associations between cardiac valve lesions and cerebrovascular manifestations in a large group of APS patients. Stroke or TIA in APS can be found as its thrombotic manifestation. Other common findings, although not part of the APS classification criteria are also valvular changes. We observed higher prevalence of TIA and valvular manifestations in SAPS patients and the frequency of the cerebrovascular and valvular manifestations in our study groups was comparable to data reported in previous studies (4,7). Possible inconsistencies in clinical presentation between patients with primary and secondary APS have not yet been thoroughly investigated. The different valvular-cerebrovascular relationships found in our study may reflect distinct pathogenic mechanisms underlying cardiac or cerebral involvements in APS patients, depending on their background autoimmune condition.

In line with our previous results published, this study also revealed statistically significant difference between patients with primary and secondary APS with respect to the aPL profile with higher prevalence in SAPS group (22). Presence of certain types of aPL is associated with increased probability of some cerebrovascular or valvular manifestations. PAPS patients who were β_2GPI IgG negative had significantly higher incidence of TIA whereas presence of β_2GPI IgG was significantly related to stroke in SAPS patients. Furthermore, β_2GPI IgG absence was significant independent risk factor for TIA in PAPS group. Accordingly, aCL and/or LA positive PAPS patients might be in higher risk of TIA development whereas presence of β_2GPI IgG might be related to more serious cerebrovascular event such as stroke. An exact pathophysiology of aPL action is not jet known and according to "two hit" hypothesis few other factors could contribute to its effect (20, 23). In the systematic review of Sciascia *et al*. based on 5217 patients and controls from 43 studies, frequency of aPL in young patients with cerebrovascular events was analysed (24). The overall aPL frequency was estimated as 17.4% (range 5–56%) for any cerebrovascular event, 17.2% (range 2–56%) for stroke and 11.7% (range 2–45%) for TIA, concluding that presence of aPL increased the risk for cerebrovascular events by 5.48-fold (95% CI 4.42 to 6.79).

As expected, age was strong predictor for stroke and TIA occurrence in groups, as well as gender (stroke more likely at male SAPS and TIA in male PAPS patients) and well known standard atherosclerotic risk factors: hypertension, hyperlipidaemia and smoking habits (25).

A possible link between heart pathology and various CNS involvements in APS has not yet been thoroughly investigated. The only cardiac-CNS association in APS to be reported thus far has been on valve vegetations as a possible risk factor for cerebral emboli. In this study we analysed the relationship between cerebrovascular and valvular manifestations in both, PAPS and SAPS group which led us to conclusion that presence of valvular changes, principally valvular vegetations, brings significant risk for TIA development in both PAPS and SAPS patients. This seems reasonable observation since valvular changes in APS patients – either valvular thickening not related to age or significant valvular incompetence as well as presence of thrombotic vegetations, occur predominantly on mitral valve, less commonly aortic valve. Vegetations situated on mitral or aortic valve have serious embolic potential leading to systemic thromboembolic events. Central nervous system is the main route for those emboli which could easily explain finding of our study. Our study also confirmed previous findings that presence of cardiac manifestations may be a risk factor for several types of CNS involvement in APS (26-38).

There are several limitations to the present study. This is single centre, retrospective, cross-sectional study which has no insight to sequence of events and advanced causatives in cerebrovascular development. Further longitudinal studies and mechanism analyses are warranted. On the other hand, the sample of APS patients studied is meaningful, giving more certainty to the recommendations provided

To conclude, valvular manifestations could be followed by serious manifestations like TIA in patients with primary APS. As a strong relationship between valvular manifestation and arterial thrombosis has been confirmed, it seems to be reasonable to direct the patient who is exhibiting valvular changes for aPL testing. Our insights bring valvular manifestations in APS to the position of significant markers of cerebrovascular events, likely on the grounds of related pathophysiology. Proper anticoagulant/antiaggregation therapy as well as vigorous action against standard atherosclerotic risk factors might delay or prevent the onset of the more serious APS manifestations, including cerebrovascular.

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