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

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Abstract

Objectives

The aim of this study was to investigate the association between non-thrombotic neurological and cardiac manifestations in patients with antiphospholipd syndrome (APS), as well as their connection with type and level of antiphospholipid antibodies.

Methods

Our prospective study comprises 333 patients: 218 with primary and 115 with secondary APS. Antiphospholipid antibody (aPL) analysis included detection of aCL(IgG/IgM), β_2GPI(IgG/IgM) and LA and served to evaluate associations with distinct neurological manifestations.

Results

The presence of aCL IgG was more common (p=0.001) in SAPS and LA in PAPS patients (p=0.002). High β_2GPI IgM levels (>100PLU/ml) were more common in epilepsy (p=0.00001) in PAPS, and in transient ischaemic attack (p=0.029) in SAPS. High β_2GPI IgG levels (>100PLU/ml) were more common in epilepsy (p=0.035) in SAPS. Chorea, migraine and epilepsy occurred more often in SAPS and headache and depression in PAPS. We found statistical significance considering the presence of aCL IgG and acute ischaemic encephalopathy in SAPS, aCL IgM and epilepsy in SAPS, aCL IgM and migraine in PAPS, β_2GPI IgG and chorea in SAPS and β_2GPI IgM and TIA and epilepsy in PAPS. LA was linked to depression, transient global amnaesia and migraine in PAPS. Patients with non-stable angina pectoris were more likely to develop TIA in both PAPS and SAPS, epilepsy and transient global amnaesia in PAPS and acute ischaemic encephalopathy in SAPS. Patients with valve vegetations were more prone to epilepsy and depression.

Conclusion

Certain aPL type and levels are associated with distinct neurological non-thrombotic manifestation, suggesting their predictive role. There is strong link between some non-thrombotic neurological and cardiac manifestations in APS patients, suggesting the complexity and evolutionary nature of APS.

Key words
antiphospholipid antibodies, non-thrombotic neurological manifestations, cardiac manifestations

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Introduction

Antiphospholipid syndrome (APS) or Huges 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, dementia, 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 aim of this study was to observe and investigate the association between non-thrombotic neurological and cardiac manifestations, in our prospective study of APS patients. Differences between patients with primary APS and APS associated to other autoimmune diseases were also analysed. This study presents the first results from our national cohort.

Materials and methods

Our study includes a total of 333 antiphospholipid syndrome patients; 218 were primary APS patients (166 female and 52 male, mean age 45.8±13.7 years), 108 had APS associated with SLE (100 female and 8 male, mean age 46.9±15.8 years) and 7 patients had APS associated with Sjögren's syndrome (6 female and 1 male, mean age 50.1±15.9 years). Among these groups there were 14 patients with catastrophic APS (CAPS), who are in an international registry of patients with catastrophic APS (CAPS Registry), created in 2000 by the European Forum on Antiphospholipid Antibodies (14, 15).

Our study is prospective. Patients with APS were included consecutively from 2000 until now. We investigated the association between non-thrombotic neurological and cardiac manifestations and we also followed other patients' pathological features – pulmonary, haematology and other – and plan to report these results soon.

All patients with SLE met the American College of Rheumatology (ACR) classification criteria (16). Disease activity was assessed at the time of enrolment in the study using of the SLEDAI score (17). Patients included in the study met the 1997 revised Sapporo criteria for APS (3). The study fulfills the ethical guidelines of the most recent declaration of Helsinki (Edinburgh, 2000) and has received approval from the local ethical committee. All patients were examined by council of rheumatologist, neurologist, neuroophthalmologist, psychiatrist, pulmonologist, cardiologist, radiologist and haematologist.

Diagnosis of neurological manifestations was established by clinical findings, followed by: electroencephalography (EEG), nuclear magnetic resonance (NMR) of endocranium and in some cases of medulla, visual, somatosensory and acoustic evoked potentials, electromyoneurography imaging and neuropsychological testing. Cognitive and memory function were compared to the performance of 50 control patients who were comparable in age but showed no signs or symptoms of systemic disease.

The diagnosis of non-stable angina pectoris was established according to the presence of chest pain, with or without ST segment and T wave ECG alterations and absence of elevated I troponin levels. In the setting of high troponin I levels with chest pain presence and/or ECG changes such as ST segment elevation or denivelation, we diagnosed

acute myocardial infarction (STEMI or NSTEMI). All enrolled patients underwent a transthoracic echocardiogram.

Laboratory tests

Lupus anticoagulant (LA) was based on the initial use of phospholipid-depleted or platelet-depleted coagulation tests, such as kaolin clotting time (KCT), dilute Russell's venom viper time (DRVVT), the tissue thromboplastin inhibition test and diluted activated partial thromboplastin time. The LA tests were not performed while the patients were receiving anticoagulant therapy. Anticardiolipin (aCL: IgG/IgM) and anti-$\beta_2$glycoprotein I (β_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).

We also followed the revised laboratory criteria for antiphospholipid syndrome (19):

- Lupus anticoagulant present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis
- Anticardiolipin antibody of IgG or IgM isotype, or both, in serum or plasma, present in medium or high titers (*i.e.* >40 GPL or MPL, or > 99th percentile) on two or more occasions, at least 12 weeks apart, measured by a standardised ELISA
- Anti-β_2-gycoprotein 1 antibody of IgG or IgM isotype, or both, in serum or plasma (in titers > 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardised ELISA

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.

Statistics

Results are presented as the mean SD, except for frequencies, which are expressed as percentages. Comparisons between groups were made by means of Mann-Whitney U-tests for continuous variables, and by chi-square analysis for categorical variables. For 2 by 2 tables Yates Correction for Continuity was used if necessary. Two-sided probability values <0.05 (2-tailed) were considered significant. All statistical analysis was performed with using SPSS version 16.0 statistical package.

Table I. Distribution of aPL in the patients with primary and APS associated to other autoimmune diseases.

	PAPS n=218 n (%)	SAPS n=115 n (%)	*p*-value
aCL IgG	78 (35.8%)	62 (53.9%)	0.001
aCL IgM	118 (54.1%)	75 (65.2%)	0.096
β_2GPI IgG	76 (34.9%)	52 (45.2%)	0.239
β_2GPI IgM	75 (34.4%)	54 (46.6%)	0.092
LA	122 (51.4%)	52 (45.2%)	0.002

PAPS: primary antiphospholipid syndrome; SAPS: secondary antiphospholipid syndrome; aCL: anticardiolipin antibodies; β_2GPI: anti-β_2 glycoprotein I antibodies; LA: lupus anticoagulant; aPL: antiphospholipid antibodies.

Table II. Comparison of frequency of non-thrombotic neurological manifestations between patients with primary and APS aassociated to other autoimmune diseases.

	PAPS/ n=218 n (%)	SAPS/ n=115 n (%)	*p*-value
Transient ischaemic attack	47 (21.6%)	31 (27%)	0.237
Chorea	0 (0%)	9 (7.8%)	0.000
Hemiballismus	0 (0%)	0 (0%)	/
Cerebellar ataxia	0 (0%)	0 (0%)	/
Epilepsy	11 (5%)	22 (19.1%)	0.001
Migraine	61 (28%)	40 (34.8%)	0.026
Transient global amnaesia	3 (1.4%)	2 (1.7%)	0.769
Acute ischaemic encephalopathy	3 (1.4%)	5 (4.3%)	0.305
Transverse myelopathy	0 (0%)	0 (0%)	/
Guillain-Barre syndrome	0 (0%)	0 (0%)	/
Anterior spinal artery syndrome	0 (0%)	1 (0.9%)	0.550
Cephalea	52 (24%)	16 (13.9%)	0.031
Vertigo	18 (8.3%)	4 (3.5%)	0.093
Depression	8 (3.7%)	0 (0%)	0.037

PAPS: primary antiphospholipid syndrome; SAPS: secondary antiphospholipid syndrome.

Results

Distribution of aPL in the patients with primary and APS associated to other autoimmune diseases is presented in Table I. It reveals that the presence of aCL IgG antibodies was significantly more common (p=0.001) in patients with SAPS and the presence of LA was significantly more common (p=0.002) in patients with primary antiphospholipid syndrome (PAPS). There was no statistically significant association between the presences of other aPL antibodies in either primary or secondary APS.

According to gender, no association between gender and non-thrombotic neurological manifestations in PAPS or SAPS was noticed.

The next step in our study was to compare the frequency of non-thrombotic neurological manifestations between patients with primary and secondary APS. Our study revealed that chorea (p<0.001), migraine (p=0.026) and epilepsy (p=0.001) occurred more often in patients with SAPS and headache (p=0.031) and depression (p=0.037) were more often in PAPS patients. Other non-thrombotic neurological manifestations occurred in both groups of patients without any statistically significant correlation (Table II).

Furthermore, we analysed association between presence of aPL antibodies with non-thrombotic neurological manifestations in both PAPS and SAPS group. Our study revealed statistical signifi-

Table III. Association between non-thrombotic neurological and cardiac manifestations in PAPS group.

PAPS patients		Transient ischaemic attack (n)			Epilepsy (n)			Transient global amnaesia (n)			Depression (n)		
		not present	present	*p*	not present	present	*p*	not present	present	*p*	not present	present	*p*
Non-stable angina pectoris	not present	158	36	**0.002**	187	7	**0.006**	193	1	**0.002**	187	6	0.217
	present	13	11		20	4		22	2		22	2	
Valve vegetations	not present	160	40	0.064	193	7	**0.001**	198	2	0.285	15	3	**0.002**
	present	11	7		14	4		17	1		194	5	

PAPS: primary antiphospholipid syndrome; n: number of patients.

Table IV. Association between nonthrombotic neurological and cardiac manifestations in SAPS group.

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

SAPS: secondary antiphospholipid syndrome; n: number of patients.

cance considering the presence of aCL IgG and acute ischaemic encephalopathy (p=0.035) in SAPS group, aCL IgM and epilepsy (p=0.030) in SAPS group, aCL IgM and migraine (p=0.016) in PAPS, β_2GPI IgG and chorea (p=0.041) in SAPS, β_2GPI IgM and transient ischaemic attack (p=0.018) and epilepsy (p=0.036) in PAPS and the presence of LA and depression (p=0.012), transient global amnaesia (p=0.049) and migraine (p=0.036) in PAPS group.

We also analysed the association between non-thrombotic neurological manifestations and non-thrombotic cardiac manifestations in both PAPS and SAPS group (Table III and IV). Patients who had unstable angina pectoris were more likely to develop transient ischaemic attack in both PAPS (p=0.002) and SAPS group (p=0.004), epilepsy (p=0.006) and transient global amnaesia (p=0.002) in PAPS and acute ischaemic encephalopathy (p=0.000) in SAPS. Patients with valve vegetations were more prone to epilepsy (p=0.001) and depression (p=0.002) in PAPS.

Finally, no association between age, smoking habits or disease duration and non-thrombotic neurological manifestations in the PAPS or SAPS group was found.

Discussion

We present the first results from our prospective study with APS patients, which started in 2000, and performed at the University Medical Centre, "Bezanijska Kosa", Belgrade, in collaboration with other clinical centres in Serbia. Besides frequent clinical manifestations of antiphospholipid syndrome, we followed less common, unusual and rare manifestations, according to Ruiz-Irastorza *et al*. (14).

This is our first, national study which investigates the influence of antiphospholipid antibody type and level on non-thrombotic neurological manifestations, as well as the association between non-thrombotic neurological and cardiac manifestations in both PAPS and SAPS group of patients. We observed many non-thrombotic neurological manifestations, both in primary and in APS associated to other autoimmune diseases patients, and determined that some of them occurred significantly more often than others in both groups of APS patients: chorea, migraine and epilepsy occurred more often in patients with SAPS, and headache and depression were more often in PAPS patients. Migraine and transient ischaemic attack were the most common clinical findings in both groups, with total prevalence of 30.3% and 23.4% patients, respectively. The frequency of the most often neurological manifestations in our study group was comparable to data reported in previous studies (4, 7, 19).

Our study revealed statistical significant difference between patients with primary and APS associated to other autoimmune diseases with respect to the presence of specific aPL. aCL IgG antibodies were statistically more frequent in patients with antiphospholipid syndrome associated to other autoimmune diseases and the presence of LA was significantly more common in patients with primary antiphospholipid syndrome (PAPS). This study also indicates that presence of certain types and levels of aPL are associated with increased probability of some nonthrombotic neurological manifestations. We found statistical significance considering the presence of aCL IgG and acute ischaemic encephalopathy in SAPS group, between presence of aCL IgM and epilepsy in SAPS and aCL IgM and migraine in PAPS group. There was a strong association between the presence of β_2GPI IgG and chorea in SAPS, between β_2GPI IgM and transient ischaemic attack and epilepsy in PAPS and between LA and depression, transient global amnaesia and migraine in PAPS.

In this study we analysed the association between non-thrombotic neurological manifestations and cardiac manifestations in both the PAPS and SAPS group and found that patients with unstable angina pectoris were more likely to develop transient ischaemic attack in both the PAPS and SAPS group, epilepsy and transient global amnaesia in PAPS and acute ischaemic encephalopathy in SAPS. Patients with valve vegetations were more prone to epilepsy

and depression in PAPS. Krause *et al*. have shown a significant association between valvular heart disease and cerebrovascular manifestations – not only stroke and TIAs, but also migraine and epilepsy (20). Our study confirmed that the presence of cardiac manifestations may be a risk factor for several types of CNS involvement in APS (21-40).

Finally, we were looking for an association between gender, age and disease duration and neurological manifestations in both the PAPS and SAPS group, which has rarely been done in previous studies. Our study showed that gender, age, smoking habits and disease duration were not associated with non-thrombotic neurological manifestations in both PAPS and SAPS patients. In this study we did not track genetic markers responsible for thrombosis, but this will be part of our next study.

In conclusion, we found that there is strong link between some non-thrombotic neurological and cardiac manifestations in APS patients, suggesting the complexity and evolutionary nature of APS.

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