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DETERMINATION OF HOMOGENOUS SUBGROUPS OF ANTIPHOSPHOLIPID SYNDROME: CLUSTER ANALYSIS BASED ON 509 CASES

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Background Antiphospholipid syndrome (APS) is a heterogeneous disease, with different phenotypes which may widely vary from classical thrombotic or obstetrical manifestations to catastrophic antiphospholipid syndrome (CAPS). APS can be associated with other auto-immune diseases, such as systemic lupus erythematosus (SLE). We aimed to determine distinct homogenous phenotypes among APS patients, using a non-supervised hierarchical cluster analysis.

Methods We performed an observational, retrospective study on APS patients satisfying Sydney classification criteria and enrolled in the French multicentre 'APS and SLE' registry. The clustering process involved an unsupervised multiple correspondence analysis followed by hierarchical ascendant clustering analysis, using 27 selected variables to widely cover APS

Abstract 029 Table 1 Main characteristics according to devised cluster (N=509)

	N available data	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P
N	509	181	130	102	96	
Demographic						
Age, mean (SD)	509	34.4 (13.3)	45.8 (15.0)	30.7 (12.6)	33.1 (13.1)	<0.001
Gender, female	509	149 (82.3)	84 (64.6)	94 (92.2)	69 (71.9)	<0.001
Classification criteria						
Arterial thrombosis	509	10 (5.5)	115 (88.5)	21 (20.6)	66 (68.8)	<0.001
Venous thrombosis	509	141 (77.9)	25 (19.2)	75 (73.5)	41 (42.7)	<0.001
Small vessel thrombosis (biopsy proven)	509	3 (1.7)	1 (0.8)	2 (2.0)	30 (31.2)	<0.001
Pregnancy morbidity [†]	396	55 (29.1)	10 (11.9)	34 (36.2)	25 (36.2)	<0.001
≥1 foetal death >10 wg [‡]	396	24 (16.1)	5 (6.0)	27 (28.7)	15 (21.7)	<0.001
≥1 premature birth <34 wg due to eclampsia, PE or placental insufficiency [†]	396	21 (14.1)	4 (4.8)	6 (6.4)	9 (13.0)	0.037
≥3 consecutive foetal losses <10 wg [‡]	396	13 (8.7)	2 (2.4)	2 (2.1)	4 (5.8)	0.053
Associated manifestations						
CAPS	509	10 (5.5)	3 (2.3)	3 (2.9)	74 (77.1)	<0.001
APS-associated nephropathy	494	2 (1.1)	4 (3.2)	7 (7.0)	88 (92.6)	<0.001
Renal hypertension	480	0 (0.0)	2 (1.6)	3 (3.0)	51 (61.4)	<0.001
Livedo reticularis	488	10 (5.7)	44 (35.2)	18 (18.8)	33 (35.9)	<0.001
Seizures	486	2 (1.1)	10 (8.0)	8 (8.4)	13 (14.3)	0.001
Migraine	486	10 (5.7)	26 (20.8)	9 (9.5)	10 (11.0)	0.001
Chorea	486	0 (0.0)	1 (0.8)	1 (1.1)	4 (4.4)	0.020
Valvular involvement	490	0 (0.0)	26 (21.1)	7 (7.2)	41 (43.6)	<0.001
Associated diseases						
SLE	509	1 (0.6)	7 (5.4)	78 (76.5)	37 (38.5)	<0.001
Other autoimmune disease*	509	4 (2.2)	12 (9.2)	31 (30.4)	8 (8.3)	<0.001
Arterial hypertension	487	14 (8.0)	60 (48.8)	11 (11.2)	45 (49.5)	<0.001
Diabetes mellitus	486	4 (2.3)	22 (17.7)	1 (1.0)	5 (5.5)	<0.001
Dyslipidaemia	485	12 (6.9)	65 (52.4)	12 (12.2)	11 (12.4)	<0.001
Biology						
Haemolytic anaemia	486	1 (0.6)	2 (1.7)	13 (13.5)	7 (7.8)	<0.001
Lymphopenia	480	5 (2.9)	7 (5.8)	22 (22.9)	2 (2.2)	<0.001
Thrombocytopenia	490	17 (9.7)	25 (20.5)	47 (48.0)	43 (45.7)	<0.001
Lupus anticoagulant	509	128 (70.7)	85 (65.4)	86 (84.3)	84 (87.5)	<0.001
Anticardiolipin antibodies	509	134 (74.0)	100 (76.9)	82 (80.4)	92 (95.8)	<0.001
Anti-β2-GPI antibodies	509	114 (63.0)	86 (66.2)	53 (52.0)	70 (72.9)	0.019
Triple positivity	509	77 (42.5)	53 (40.8)	46 (45.1)	63 (65.6)	0.001
ANA	432	71 (51.1)	63 (59.4)	98 (98.0)	71 (81.6)	<0.001
Low C3	286	8 (9.3)	15 (21.1)	51 (65.4)	28 (54.9)	<0.001

Data are expressed as number (% of available data) unless stated otherwise.

Comparisons between different subgroups were performed with Chi-2 tests and ANOVAs.

[†]Percentage of obstetrical manifestations were calculated among women only.

*Other autoimmune diseases included Sjögren syndrome, systemic sclerosis, rheumatoid arthritis, or chronic lymphocytic thyroiditis.

Abbreviations: N=number; wg=weeks of gestation; PE=preeclampsia; SLE=systemic lupus erythematosus; ANA=anti-nuclear antibody.

clinical and biological manifestations. Comparisons between different subgroups were performed with Chi-2 tests and ANOVAs.

Results We included 509 patients in the analyses, mainly women (78%). Mean ($\pm$ SD) age at APS diagnosis was 36.3 ± 14.7 years, and mean follow-up duration after APS diagnosis was 10.3 ± 8.5 years. Cluster hierarchical classification yield in four homogenous groups of patients. Their main characteristics are described in Table 1.

1. Cluster 1 (n=181) included mostly patients with venous thrombosis (78%) and premature births due to placenta insufficiency (14%) history, without associated auto-immune disease (only 2.2%).
2. Cluster 2 (n=130) included older patients (mean 45.8 years), less frequently women (65% of women), with arterial events history (89%). Valvular involvement (21%), migraine (21%), livedo (35%), arterial hypertension (49%), and cardiovascular risk factors were relatively frequent.
3. Cluster 3 (n=102) included younger patients, frequently women (mean 30.7 years; 92% women), with associated SLE (76%) or other autoimmune diseases (30%). They frequently had history of venous thrombosis (74%) and of pregnancy morbidity (36%). Thrombocytopenia (48%), haemolytic anaemia (14%), and lupus anticoagulant (84%) were frequent.
4. Cluster 4 (n=96) included mainly patients with a history of CAPS (77%) and/or APS-associated nephropathy (93%), and pregnancy morbidity (36%). Renal hypertension (61%), livedo (36%), seizures (14%), valvular involvement (44%) and triple positivity (66%) were relatively frequent.

Conclusions Using an unsupervised clustering method, our study highlighted four distinct homogenous subgroups of APS patients that were predominantly venous; arterial; associated with SLE or other autoimmune disease; and microthrombotic. It confirms the underlying idea of heterogeneous pathophysiological mechanisms.

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COMPLEMENT DEPOSITION, C4d, ON PLATELETS IS ASSOCIATED WITH VASCULAR EVENTS AND ANTIPHOSPHOLIPID ANTIBODIES IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Objective Complement components, including C4d, can be found on activated platelets, a process associated with vascular

disease in systemic lupus erythematosus (SLE). We investigated whether platelet C4d (PC4d) adds additional value to traditional and known lupus-associated risk factors when identifying SLE patients with vascular disease.

Method This cross-sectional study, included 308 well-characterized SLE patients and 308 matched general population controls. PC4d deposition was analyzed using flow cytometry. Values >95% of controls were considered as PC4d positive (+). Antiphospholipid antibodies (aPL) were determined by Luminex, and the lupus anticoagulant (LA) test was performed by the DRVVT test. History of vascular disease (composite and as separate outcomes) was defined at inclusion.

Results SLE patients had increased PC4d deposition as compared to population controls (50% versus 5%, $p < 0.0001$). PC4d+ positively associated with any vascular events, and separately with venous and cerebrovascular events, and also with all investigated aPL profiles. The association for any vascular event remained statistically significant after adjustment for traditional and SLE-associated risk factors (OR:2.4, 95% CI 1.3–4.6, $p = 0.006$). Compared to patients negative for both PC4d and LA, patients with double positivity were more likely to have vascular disease (OR:12.0, 95% CI 5.4–28.3; attributable proportion due to interaction 0.7, 95% CI 0.4–1.1) (figure 1).

Abstract O30 Figure 1 Interaction analysis between PC4d and Lupus Anticoagulant Interaction between complement C4d deposition (PC4d) and lupus anticoagulant (LA), after adjustment for age (in 10 years), sex, hypertension, estimated glomerular filtration rate (eGFR) according to Modification of Diet in renal Disease (MDRD, per 10 units), and smoking, on the odds of vascular disease (arterial and/or venous) in individuals with systemic lupus erythematosus. RERI = relative excess risk due to interaction; AP = attributable proportion due to interaction. See supplementary material for figures.

Conclusions PC4d+ is associated with vascular events in SLE, independently of traditional and SLE-associated risk factors. Concurrent presence of PC4d and LA seem to interact to further increase the odds for vascular events. Prospective studies should examine whether the aPL/PC4d combination can improve prediction of vascular events in SLE and/or APS.