The Clinical Spectrum of Catastrophic Antiphospholipid Syndrome in the Absence and Presence of Lupus

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ABSTRACT. ***Objective.*** To compare the clinical spectrum of patients with primary catastrophic antiphospholipid syndrome (P-CAPS) to those with systemic lupus erythematosus-associated CAPS (SLE-CAPS).

Methods. We used the Internet-based CAPS Registry to compare the demographic, clinical, and laboratory characteristics of 127 P-CAPS patients to 103 SLE-CAPS patients. In a logistic regression analysis, we also determined the poor prognostic factors for mortality.

Results. At the time of CAPS diagnosis, compared to patients with P-CAPS, those with SLE-CAPS were more likely to be female and younger; have cerebral and pancreatic involvement; receive corticosteroids and cyclophosphamide; demonstrate a lower prevalence of high titer (≥ 80 U) IgG anticardiolipin antibody; and have a higher risk for mortality after adjusting for age, sex, organ involvement, and treatment. Based on a logistic regression analysis, cyclophosphamide use was associated with increased mortality in P-CAPS but improved survival in SLE-CAPS patients.

Conclusion. SLE is a poor prognostic factor in patients with CAPS and cyclophosphamide may be beneficial in those with SLE-CAPS. (J Rheumatol 2007;34:346–52)

Key Indexing Terms:

CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME
ANTIPHOSPHOLIPID SYNDROME
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ANTICARDIOLIPIN ANTIBODIES
SYSTEMIC LUPUS ERYTHEMATOSUS
ASHERSON'S SYNDROME

Antiphospholipid syndrome (APS) is characterized by vascular thromboses (arterial or venous) and/or pregnancy morbidity occurring in the presence of antiphospholipid antibodies (aPL), most commonly a positive lupus anticoagulant (LAC) test, anticardiolipin antibodies (aCL), and anti-$ß_2$-glycoprotein I antibodies (anti-$ß_2$-GPI)[1]. The clinical spectrum of aPL ranges from asymptomatic individuals (with no aPL-related clinical manifestations) to those with multiple organ thromboses and failure developing over a short period, also known as catastrophic APS (CAPS)[2,3]. Encountered in less than 1% of patients with APS, CAPS is characterized by accelerated widespread small/medium vessel thromboses with unusual organ involvement and has a mortality of almost 50% despite aggressive multimodal intensive treatment[4,5]. An international consensus statement on preliminary criteria for the diagnostic classification of CAPS has been published to provide a uniform diagnostic approach to patients with CAPS[6].

The diagnosis of CAPS may be challenging, as it shares clinical features with other life-threatening conditions such as sepsis, disseminated intravascular coagulation, heparin-induced thrombocytopenia, or other thrombotic microangiopathies [thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, and HELLP syndrome (hemolytic anemia, elevated liver enzymes, low platelet count)]. Nonetheless, early recognition of CAPS is crucial; as soon as the diagnosis is suspected, patients should receive anticoagulation and corticosteroids (first-line therapies), with the addition of plasma exchange or intravenous immunoglobulin (IVIG) (second-line therapies) in the presence of poor prognostic factors and/or lack of response[6]. In the case of deteriorating clinical situation, a third-line treatment (such as cyclophosphamide or rituximab) is recommended[7].

APS can occur in the absence [primary APS (P-APS)] or presence of an autoimmune connective tissue disorder (CTD). Systemic lupus erythematosus (SLE)[8] is the most common CTD associated with APS; in a cohort of 1000 patients with APS, 53% of patients had P-APS while 36% had APS associated with SLE (SLE-APS)[5]. In this cohort, patients with SLE-APS more commonly had arthritis, livedo reticularis, thrombocytopenia, and leukopenia. Although there have been reports of patients with SLE developing CAPS[9], the clinical spectra and the outcomes of patients with CAPS in the absence and presence of SLE have not been well documented.

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We compared the demographic, clinical, and laboratory characteristics of patients with P-CAPS to those with SLE-CAPS. Secondarily, we also examined the poor prognostic factors in both groups that can affect mortality.

MATERIALS AND METHODS

Patient identification. We identified patients through the international Web-based CAPS Registry (details of the registry can be found at www.med.ub.es/MIMMUN/FORUM/CAPS.HTM), to which there is free access. Patients with a CAPS diagnosis have been included in this registry since 2000 through published or voluntary physician reports. Although patients have been included in the registry from multiple centers over an extended period of time, 51% of patients fulfilled the classification criteria for "definite" CAPS and an additional 40% for "probable" CAPS[10].

Selected variables for analysis. We compared the demographic, clinical, and laboratory characteristics of patients with P-CAPS to those with SLE-CAPS; we excluded patients with lupus-like disease or autoimmune diseases other than SLE.

Demographic characteristics that were retrieved from the registry included sex and mean age at the time of CAPS diagnosis.

Clinical characteristics that were retrieved from the registry included precipitating factors, prior APS diagnosis, type of organ involvement (Table 1), treatment modalities, and mortality. The registry includes organ involvement data (depending on the availability of information) based on clinical signs/symptoms, radiological studies, and/or biopsy results. While comparing cardiac, pulmonary, cerebral, renal, and cutaneous involvement, 3 analyses were performed for each organ system: (1) any thrombotic event; (2) only nonthrombotic events; and (3) any event.

Laboratory characteristics that were retrieved from the registry included the presence of thrombocytopenia, hemolysis, schistocytes, Coombs positive hemolytic anemia, fibrin degradation products, D-dimer, and positive antinuclear (ANA) and anti-double-stranded DNA antibody (anti-dsDNA) tests. In addition, LAC test (positive or negative), aCL IgG/IgM levels (negative, < 20 U; low positive, 20–39 U; moderate positive, 40–79 U; or high positive, ≥ 80 U), and fibrinogen levels (low, normal, or high) were analyzed. Of note, positive aCL tests with unknown titers were excluded from the analysis.

Statistical methods. Student's t test and Pearson's chi-square test without Yates' correction were used for univariate analysis (SPSS 11.0; SPSS Inc., Chicago, IL, USA) while comparing the demographic, clinical, and laboratory characteristics of patients with P-CAPS and SLE-CAPS. Poor prognostic factors for mortality were analyzed both combined and independently in patients with P-CAPS and SLE-CAPS by univariate analysis and logistic regression (EpiInfo; CDC, Atlanta, GA, USA). Logistic regression model included age, sex, SLE diagnosis, clinical manifestations that were found to affect mortality on the univariate analysis, thrombocytopenia, and the most commonly used treatments (anticoagulation, corticosteroids, IVIG, plasma exchange, cyclophosphamide, hemodialysis).

Table 1. Organ involvement data included in the CAPS Registry.

Peripheral	
Arterial	Femoral, iliac, aorta, subclavian, radial, posterior tibial, dorsalis pedis, brachial, cubital, or ulnar thromboses
Venous	Deep venous, iliac, inferior vena cava, jugular, popliteal, superficial femoral, axillary, or brachiocephalic thromboses
Cardiac	
Thrombotic	Myocardial infarction, microinfarcts, or coronary, atrial or right ventricle thromboses
Nonthrombotic	Valve lesions, Libman-Sachs, cardiomyopathy, or cardiomegaly
Pulmonary	
Thrombotic	Pulmonary emboli, microthrombosis, or infarcts
Nonthrombotic	Acute respiratory distress syndrome, infiltrate, edema, or hemorrhage
Cerebral	
Thrombotic	Cerebrovascular accident, transient ischemic attack, infarcts, thromboses (micro and macro), venous sinus thrombosis
Nonthrombotic	Seizure, encephalopathy, or hemorrhage
Renal	
Thrombotic	Renal arterial and venous thrombosis, infarcts, or ischemia
Nonthrombotic	Glomerulonephritis, renal failure, proteinuria, hematuria, or interstitial nephritis
Skin	
Thrombotic	Ulcer, gangrene, necrosis, ischemia, or thrombosis
Nonthrombotic	Livedo-reticularis, purpura, cyanosis, Raynaud's phenomenon, ecchymosis, erythema nodosum, epidermolysis bullosa
Hepatic	Microthrombi, elevated liver enzymes, Budd-Chiari, or hepatic vein or portal vein thrombosis
MGI	Microthrombi, hemorrhage, ischemia, or perforation
Splenic	Arterial and venous thromboses, infarct, or splenomegaly
Adrenal	Hemorrhage, infarct, vein thrombi, or Addison's disease
Hematological	Thrombotic microangiopathic hemolytic anemia or disseminated intravascular coagulation
Pancreas	Microthrombi and pancreatitis
Gall bladder	Microthrombi and cholecystitis
Retinal	Arterial and venous thrombi
Bone marrow	Infarct and pancytopenia

MGI: mesentero-gastrointestinal.

RESULTS

The registry included 262 patients as of September 1, 2005. One hundred twenty seven (49%) patients had P-CAPS and 103 (39%) had SLE-CAPS; we excluded 13 patients with lupus-like disease and 19 with autoimmune diseases other than SLE. Table 2 shows demographic and selected clinical characteristics of patients; SLE-CAPS patients were more likely to be female and younger at the time of CAPS diagnosis. CAPS was the first manifestation of APS in almost half of the P-CAPS and SLE-CAPS patients. Table 3 shows the identified precipitating factors at the time of CAPS event; infec-

Table 2. Selected demographic and clinical characteristics in patients with P-CAPS and SLE-CAPS.

Characteristics	P-CAPS (n = 127), n (%)	SLE-CAPS (n = 103), n (%)
Male*	50 (39)	15 (15)
Age at diagnosis*, mean yrs ± SD	39.4 ± 15.0	32.3 ± 12.1
Presence of precipitating factors	63 (50)	63 (61)
CAPS as the first manifestation of APS	57 (45)	47 (46)
Mean number of organs involved, ± SD	4.13 ± 0.14	4.46 ± 0.15
Mortality*	44 (35)	60 (58)

* $p < 0.001$, APS: antiphospholipid syndrome; P-CAPS: primary catastrophic antiphospholipid syndrome; SLE-CAPS: systemic lupus erythematosus associated CAPS.

Table 3. Precipitating factors in patients with P-CAPS and SLE-CAPS. Five patients with P-CAPS and 8 patients with SLE-CAPS had 2 identified precipitating factors.

Precipitating Factor	P-CAPS (n = 127), n (%)	SLE-CAPS (n = 103), n (%)
Infection*	18 (14)	30 (29)
Surgery	19 (15)	10 (10)
Obstetrical	8 (6)	6 (6)
Anticoagulation withdrawal	7 (5)	7 (7)
Malignancy**	10 (8)	2 (2)
Lupus flare	0 (0)	9 (9)
Oral contraceptives	4 (3)	1 (1)
Other medications	2 (2)	6 (6)
Unknown	64 (50)	40 (39)

* p = 0.006; ** p = 0.044.

tions were statistically more common, whereas malignancies were statistically less common in patients with SLE-CAPS.

The incidence of organ system involvement was similar in patients with P-CAPS and SLE-CAPS except any cerebral and pancreatic involvement, which were more common in patients with SLE-CAPS (Table 4). The subanalysis of cerebral involvement based on thrombotic and nonthrombotic involvement did not demonstrate a statistical difference between the groups.

Table 4. Comparison of organ involvement in patients with P-CAPS and SLE-CAPS.

Organ	P-CAPS (n = 127), n (%)	SLE-CAPS (n = 103), n (%)
Peripheral (any)	42 (33)	31 (30)
Arterial	16 (13)	12 (12)
Venous	31 (24)	21 (20)
Cardiac (any)	57 (45)	42 (41)
Thrombotic	31 (24)	29 (28)
Nonthrombotic	26 (21)	13 (13)
Pulmonary (any)	77 (61)	69 (67)
Thrombotic	41 (32)	34 (33)
Nonthrombotic	36 (28)	35 (34)
Cerebral (any)*	68 (54)	71 (69)
Thrombotic	60 (47)	61 (59)
Nonthrombotic	8 (6)	10 (10)
Renal (any)	85 (67)	74 (72)
Thrombotic	34 (27)	38 (37)
Nonthrombotic	51 (40)	36 (35)
Skin (any)	58 (46)	55 (53)
Thrombotic	31 (24)	33 (32)
Nonthrombotic	27 (21)	22 (21)
Hepatic	40 (32)	31 (30)
MGI	29 (22)	22 (21)
Splenic	21 (16)	20 (19)
Adrenal	16 (13)	10 (10)
TMHA	12 (9)	9 (9)
DIC	14 (11)	13 (13)
Pancreas**	5 (4)	12 (12)
Gall bladder	5 (4)	4 (4)
Retinal	11 (9)	6 (6)
Bone marrow	8 (6)	3 (3)

* p = 0.018; ** p = 0.026. MGI: mesentero-gastrointestinal; TMHA: thrombotic microangiopathic hemolytic anemia; DIC: disseminated intravascular coagulation.

Treatment modalities used in patients with CAPS are shown in Table 5; corticosteroids and cyclophosphamide were used more frequently in patients with SLE-CAPS. Forty-four of 127 (35%) P-CAPS and 31 of 103 (30%) SLE-CAPS patients received a combination of anticoagulation, corticosteroids, and IVIG or plasma exchange.

Table 6 shows the laboratory characteristics of patients

Table 5. Treatment modalities used in patients with P-CAPS and SLE-Caps. Treatment data were not available for one P-CAPS patient.

Modality	P-CAPS (n = 126), n (%)	SLE-CAPS (n = 103), n (%)
Antiplatelet agents	14 (11)	9 (9)
Anticoagulation	108 (86)	78 (76)
Corticosteroid*	83 (66)	89 (86)
Cyclophosphamide*	19 (15)	48 (47)
Plasma exchange	40 (32)	26 (25)
Hemodialysis	24 (19)	16 (16)
IVIG	23 (18)	24 (23)
Fibrinolytics	7 (6)	1 (1)

* p < 0.001, IVIG: intravenous immunoglobulin.

Table 6. Laboratory findings in patients with P-CAPS and SLE-CAPS.

Finding	P-CAPS, n^+/n (%)	SLE-CAPS, n^+/n (%)
Thrombocytopenia	72/117 (62)	66/97 (68)
Hemolysis	32/109 (29)	39/95 (41)
Schistocytes	17/90 (19)	9/82 (11)
Coombs-positive	11/34 (32)	18/34 (53)
High FDP	13/20 (65)	8/13 (62)
High D-dimer	6/13 (46)	9/12 (75)
Fibrinogen level		
Low	1/24 (4)	4/20 (20)
Normal	11/24 (45)	11/20 (55)
High	12/24 (50)	5/20 (25)
aCL-IgG titer		
Negative	22/85 (26)	20/69 (29)
Low	7/85 (8)	8/69 (12)
Moderate	13/85 (15)	19/69 (28)
High*	43/85 (51)	22/69 (31)
aCL-IgM titer		
Negative	66/89 (74)	48/69 (70)
Low	7/89 (8)	3/69 (4)
Moderate	5/89 (6)	7/69 (10)
High	11/89 (12)	11/69 (16)
aCL-IgG/M titer		
Moderate to high	61/70 (87)	46/54 (85)
Positive LAC test	98/120 (82)	62/84 (74)
ANA**	34/103 (33)	75/89 (84)
Anti-dsDNA**	3/87 (3)	60/89 (67)

n^+/n: Number of patients with the specified laboratory finding/number of patients tested. * p = 0.019; ** p < 0.001. FDP: Fibrin degradation products; LAC: lupus anticoagulant.

with P-CAPS and SLE-CAPS. The presence of aPL and thrombocytopenia were the most common laboratory findings in both groups. No aPL profile difference was found between 2 groups except the higher prevalence of high titer (≥ 80 U) IgG aCL in patients with P-CAPS. Positive ANA and anti-dsDNA tests were significantly more common in patients with SLE-CAPS.

Mortality of P-CAPS and SLE-CAPS patients combined was 45% at the time of CAPS presentation. Overall, the highest survival rate was achieved with the combination of anticoagulation, corticosteroids, and plasma exchange (72%). The highest survival rate was achieved in patients with SLE–CAPS who received anticoagulation, corticosteroids and plasma exchange (65%), and in patients with P-CAPS who received anticoagulation, corticosteroids and IVIG (82%).

Poor prognostic factors for mortality identified by the combined univariate analysis of P-CAPS and SLE-CAPS patients were: age over 36 years, SLE diagnosis, any/thrombotic pulmonary, any/thrombotic renal and/or adrenal involvement, higher number of organs involved (3.95 in survived vs 4.66 in expired patients; $p < 0.001$), and hemodialysis. The presence of thrombocytopenia and anticoagulation treatment were associated with better outcomes. Of note, patient's sex did not have any effect on mortality. In a logistic regression analysis, age over 36 years, SLE diagnosis, the involvement of any pulmonary, any renal and adrenal organ systems, thrombocytopenia, and treatment with anticoagulation, hemodialysis, and/or plasma exchange had significant effects on mortality (Table 7).

Poor prognostic factors for mortality by univariate analysis in P-CAPS patients were: age over 36 years, any/thrombotic pulmonary, any/thrombotic renal involvement, higher number of organs involved (3.86 in survived vs 4.64 in expired patients; $p = 0.005$), treatment with cyclophosphamide, and hemodialysis. The presence of high fibrinogen levels and anticoagulation treatment were associated with better outcomes. In patients with SLE-CAPS, age, renal involvement, number of organs involved, high fibrinogen levels, and hemodialysis had no effect on mortality; whereas adrenal involvement was associated with higher mortality, and thrombocytopenia and cyclophosphamide treatment were associated with decreased mortality (data not shown). In a logistic regression analysis, we found that any renal involvement, anticoagulation, cyclophosphamide, and hemodialysis had significant effect on prognosis in patients with P-CAPS, while any pulmonary involvement, thrombocytopenia, anticoagulation, and cyclophosphamide had significant effect on prognosis in patients with SLE-CAPS (Table 8).

DISCUSSION

In our analysis of the CAPS Registry, in which we compared the clinical characteristics of patients with P-CAPS to those with SLE-CAPS, we found that SLE-CAPS patients are more likely to: (1) be female and younger; (2) have cerebral and pancreatic involvement; (3) receive corticosteroids and cyclophosphamide; (4) demonstrate a lower prevalence of high IgG aCL; and (5) have a higher risk for mortality after adjusting for age, sex, organ involvement, and treatment.

Cervera, *et al* reported a female-to-male ratio of 7:1 in SLE-APS and 3.5:1 in P-APS patients[5]; Moss and Isenberg demonstrated that SLE-APS patients are diagnosed with APS at an earlier age than P-APS patients[11]. Our analysis of the CAPS registry was consistent with these studies; we found that female-to-male ratio was 8.5:1 in SLE-CAPS and 1.5:1 in P-CAPS patients, with a CAPS event occurring at a significantly younger age in SLE-CAPS patients. This younger onset of CAPS event in patients with SLE-CAPS can be attributable to the early-age onset of SLE and/or increased incidence of thrombosis in SLE patients independent of aPL[12]. Of particular note, a history of "triggering" factor may be obtained in

Table 7. Prognostic factors in patients with P-CAPS and SLE-CAPS combined (univariate and multivariate analysis, n = 230).

Variable	Univariate Analysis (Prevalence)			Multivariate Analysis*	
	Death (%)	Survived (%)	p	OR (95% CI)	p
Age > 36 yrs	56	38	0.007	2.58 (1.26–5.28)	0.009
Male	28	29	0.908	0.83 (0.37–1.83)	0.638
SLE	58	34	< 0.001	2.82 (1.31–6.09)	0.008
Any pulmonary involvement	75	54	0.001	4.00 (1.79–8.93)	0.001
Any renal involvement	79	61	0.004	2.88 (1.30–6.35)	0.009
Adrenal involvement	17	6	0.009	3.07 (1.02–9.22)	0.045
Thrombocytopenia	57	71	0.030	0.38 (0.18–0.80)	0.011
Anticoagulation	69	91	< 0.001	0.14 (0.05–0.39)	< 0.001
Corticosteroids	76	74	0.786	0.90 (0.36–2.24)	0.823
IVIG	19	22	0.658	0.82 (0.34–1.95)	0.649
Plasma exchange	23	34	0.080	0.36 (0.14–0.92)	0.033
Cyclophosphamide	33	26	0.297	1.02 (0.46–2.30)	0.952
Hemodialysis	23	13	0.041	3.58 (1.21–10.65)	0.022

OR: Odds ratio for mortality; IVIG: intravenous immunoglobulin.

Table 8. Comparison of prognostic factors in patients with P-CAPS and SLE-CAPS by multivariate analysis.

Variable	P-CAPS, n = 127 OR (95% CI)	p	SLE-CAPS, n = 103 OR (95% CI)	p
Age > 36 yrs	2.08 (0.75–5.75)	0.156	2.93 (0.82–10.51)	0.098
Male	1.73 (0.61–4.91)	0.305	0.41 (0.08–2.14)	0.291
Any pulmonary involvement	2.89 (0.91–9.12)	0.071	14.07 (2.64–74.91)	0.002
Any renal involvement	3.51 (1.08–11.42)	0.037	3.19 (0.81–12.51)	0.097
Adrenal involvement	1.43 (0.34–6.01)	0.626	13.41 (0.80–226.26)	0.072
Thrombocytopenia	0.53 (0.18–1.59)	0.259	0.09 (0.02–0.39)	0.001
Anticoagulation	0.18 (0.04–0.82)	0.027	0.06 (0.01–0.34)	0.001
Corticosteroids	0.77 (0.23–2.59)	0.668	1.40 (0.15–12.95)	0.766
IVIG	0.34 (0.08–1.51)	0.155	0.94 (0.22–4.02)	0.929
Plasma exchange	0.28 (0.07–1.16)	0.079	0.36 (0.08–1.59)	0.177
Cyclophosphamide	8.50 (1.91–37.83)	0.005	0.20 (0.06–0.71)	0.013
Hemodialysis	5.41 (1.22–23.88)	0.026	2.80 (0.46–17.17)	0.264

IVIG: intravenous immunoglobulin.

50% of patients[4], and we found a higher prevalence of infections as precipitating factors in SLE-CAPS patients, which is most likely due to the longterm immunosuppressive therapy that SLE patients receive.

In this cohort, patients with SLE-CAPS were more likely to develop cerebral involvement, although this association was lost when thrombotic and nonthrombotic events were independently analyzed. A possible explanation for increased incidence of cerebral events in SLE-CAPS patients is the increased incidence of non-aPL causes of cerebral involvement in SLE patients, such as accelerated atherosclerosis, antiribosomal-P protein antibodies[13], oxidative stress, or the intrathecal production of proinflammatory cytokines[14]. Further, despite its unclear etiopathogenesis, pancreatitis can occur in patients with SLE; although based on small numbers, we found that the prevalence of pancreatitis in SLE-CAPS patients was higher compared to P-CAPS patients.

Corticosteroid and cyclophosphamide combination is commonly used in the management of the life-threatening manifestations of lupus. Thus, it was not surprising to find in our cohort that SLE-CAPS patients had received both corticosteroids and cyclophosphamide more often than P-CAPS patients (confounding by indication). Although decreased corticosteroid usage in P-CAPS patients can be explained by the delayed CAPS diagnosis, based on our clinical experience, we believe that all CAPS patients should receive corticosteroids, as systemic inflammatory response syndrome is a critical component of CAPS and the administration of corticosteroids has been shown to reduce nuclear factor-κB (NF-κB) translocation leading to reduced cytokine production[15]. Of note, it was also recently reported that aPL increase tissue factor transcription, expression, and function as well as interleukin 6 (IL-6) and IL-8 upregulation via NF-κB and p38 mitogen-activated protein kinase[16].

We also observed that cyclophosphamide had a worsening effect on the prognosis of patients with P-CAPS, whereas it was associated with increased survival in those with SLE-CAPS. Although 19 patients with P-CAPS who were treated with cyclophosphamide had a higher mean number of organs involved than those who had not received this therapy (5.2 vs 3.9; p = 0.001), considering a better prognosis in SLE-CAPS patients who received cyclophosphamide, it may be an effective additional treatment in SLE-CAPS patients, especially in the presence of active lupus manifestations.

Cervera, *et al* reported the prevalence of thrombocytopenia and leukopenia to be higher in patients with SLE-APS when compared to those with P-APS[5]. However, we found no difference between the laboratory characteristics of P-CAPS and SLE-CAPS patients except the higher incidence of high aCL-IgG titers in P-CAPS patients (an association that was lost during the combined analysis of moderate to high titers of aCL IgG/IgM) and the higher incidence of ANA and anti-dsDNA in SLE-CAPS patients.

Our study showed that the presence of lupus in patients with CAPS is a poor prognostic factor for mortality after adjusting for age, sex, organ involvement, and treatment. Further, organ involvement except pulmonary system, laboratory measures except thrombocytopenia, and treatment except anticoagulation and/or cyclophosphamide had no effects on mortality in patients with SLE-CAPS. This increased mortality in patients with SLE-CAPS can be attributed to already present lupus-related disease activity and/or organ damage; the design of the study did not allow us to analyze cumulative SLE activity prior to CAPS diagnosis. Further, prognostic factors for mortality in our cohort were different for P-CAPS and SLE-CAPS patients except the use of anticoagulation, which improved the prognosis in all patients with CAPS. The unknown severity of thrombocytopenia in the CAPS registry makes the positive association between thrombocytopenia and better outcomes clinically less reliable. The association between poor prognosis and hemodialysis in P-CAPS patients is likely due to severe renal failure that necessitates this treatment modality.

Our study is based on a Web-based registry of a cohort of

CAPS patients, with some limitations. First, the registry data were collected retrospectively and by voluntary physician report, which makes our study vulnerable to ascertainment bias. However, patients only qualify for registration after confirmation of diagnosis by the CAPS registry committee members, enhancing data quality. Second, all the involved organ systems might have not been fully appreciated in all patients since an autopsy was not performed systematically. Finally, certain laboratory tests were not available for all patients. Despite these limitations, ours is the first detailed report comparing the clinical characteristics of patients with P-CAPS to those with SLE-CAPS.

In summary, the presence of SLE is a poor prognostic factor in patients with CAPS. An early aggressive multimodal approach to patients with SLE-CAPS, possibly with the inclusion of cyclophosphamide, may improve outcomes.

APPENDIX: The Catastrophic Antiphospholipid Syndrome Registry Project Group (European Forum on Antiphospholipid Antibodies).

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