ORIGINAL ARTICLES

Clinical manifestations and vascular events in patients with lupus erythematosus anticardiolipin antibodies and Raynaud's phenomenon

VANESSA E. RODRIGUEZ, MD*; ESTHER N. GONZALEZ-PARES, MD†; CYNTHIA RIVERA, MPH‡

Background: **Raynaud's phenomenon (RP) and anticardiolipin antibodies (ACL) are two common clinical manifestations in patients with systemic lupus erythematosus (SLE). RP may lead to digital or limb loss. ACL are associated to thrombotic episodes. It is not yet clear if there is an association between RP and the presence of ACL in patients with SLE.**

Objectives: **To study if the presence of both RP and ACL in patients with SLE may be associated with certain clinical manifestations or thrombotic events compared to SLE patients without RP or ACL.**

Methods: **SLE patients from two lupus clinics were recruited. The patients were divided into 4 groups. Patients with RP and positive ACL (RP+ ACL+), patients with RP but negative ACL (RP+ ACL-), patients with negative RP and positive ACL (RP- ACL+), and patients that were negative for RP and ACL (RP- ACL-) used as the control group. Demographic data, diagnostic criteria, clinical manifestations, history of arterial thrombosis, venous thrombosis and abortions were recorded. A physical examination was done. Anticardiolipin antibodies IgG and IgM were done in the rheumatology laboratory at the University of Puerto Rico School of Medicine. Descriptive statistics as well as analysis of variances (ANOVA), and polytomous logistic regression were used.**

Results: **236 patients with SLE were studied. There was a tendency toward an increase in arterial thrombosis (p-value= 0.094) and venous thrombosis (p-value= 0.067) in the group that were positive for RP and ACL (RP+ ACL+). Although it was not statistical significant, when polytomous logistic regression was used, both arterial and venous thrombosis had an increase in relative risk 3.21 for arterial and 3.11 for venous thrombosis. Abortions were not increased in any of the four groups. Clinical manifestations from SLE did not differ among the four groups.**

Conclusions: **Patients with both RP and ACL seem to be at an increase risk for both arterial and venous thrombotic events; these patients may benefit from an antiplatelet medication to prevent these events to occur.**

Key words: Systemic lupus erythematosus Anticardiolipin antibodies Venous thrombosis Arterial thrombosis

Systemic lupus erythematosus (SLE) is a complex autoimmune disorder with a wide spectrum of clinical manifestations and multisystemic involvement (1). Raynaud's phenomenon (RP) occurs commonly in SLE, present in up to 40% of patients (2). RP is a common vasospastic disorder that in the absence of a systemic illness is usually benign, but in patients with SLE it may lead to digital ulcers and gangrene (3-5).

*Associate Professor, Rheumatology Section, Department of Internal Medicine, University of Puerto Rico School of Medicine, †Professor, Rheumatology Section, Department of Internal Medicine, University of Puerto Rico School of Medicine ‡Instructor, Department of Internal Medicine, University of Puerto Rico School of Medicine, Biostatistical Core Manager RCMI Clinical Research Center

Address for correspondence: Vanessa E. Rodriguez MD, University of Puerto Rico Medical Sciences Campus, Division of Rheumatology, Department of Internal Medicine, PO Box 365067, San Juan, Puerto Rico 00936-5067, Telephone: (787) 764-6839 or (787) 758-2525 ext 1649 or 1825, Fax: (787) 764-6839, Email: varodriguez@rcm.upr.edu

Another factor that may contribute to gangrene in patients with SLE is the presence of anticardiolipin antibodies (ACL). ACL may cause thrombosis in SLE by direct endothelial damage, antibody mediated platelet activation, and inhibition of endogenous anticoagulants (6).

ACL are seen in 30-44% of SLE patients, and may have multiple manifestations such as digital gangrene, venous thrombosis, arterial thrombosis, abortions, and thrombocytopenia (6-9).

In patients with SLE and ACL, thrombotic events have been observed in 25%- 40% of patients compared to 7-18% of thrombotic events in SLE patients without ACL (6, 9).

However, very few studies have examined if there is an association between the presence of RP and ACL in SLE patients (10-12). The aim of this study is to determine whether the presence of PR and ACL in patients with SLE

is associated with specific clinical manifestations and thrombotic events as compared to SLE without RP nor ACL.

Material and Methods

The study included patients with SLE attending an outpatient SLE clinic conducted by the Rheumatology Section of the UPR School of Medicine and a private rheumatology clinic. The UPR School of Medicine is a tertiary referral center for the entire island of Puerto Rico. The majority of the patients seen at the School of Medicine have no private insurance, but are covered by a government paid HMO insurance, so they need a referral from their primary doctor to attend our clinic. The private practice population patients also come from the entire island and all have private insurance.

The patients were recruited between May 2000 to May 2004. A total of 236 patients were included in the study. All patients fulfilled the American College of Rheumatology revised criteria for the classification of SLE (13).

Four groups were studied: patients with RP and positive ACL, patients with RP and negative ACL, patients without RP and positive ACL, patients without RP and negative ACL (control group).

Two rheumatologists worked in the study and enrolled all subjects. The patients were classified as having RP if documented by history, physical examination or medical record. RP was defined as episodic digital pallor with sequential change of color from pallor to cyanosis to erythema when exposed to cold (14).

This is a cross-sectional study, in which patients were interview on one occasion. After identifying the subjects, they were invited to participate in the study and an informed consent was taken.

The variables included demographics, clinical manifestations, vascular events and presence of the anticardiolipin antibodies.

Demographics included the gender, age, years with SLE, smoking (defined if the patient ever smoked), hypertension (defined as systolic blood pressure >140 mm/Hg, and diastolic blood pressure >90) and diabetes mellitus. Clinical manifestations variables were arthralgia/arthritis (defined as having joint pains or joint swellings), malar rash (defined as rash on malar area of face lasting more than 24 hours and unrelated to sun exposure), discoid rash (defined as having diagnosis of discoid rash by a dermatologist), oral ulcers (defined as presence of non-painful ulcers on mouth mucosa), photosensitivity (defined as developing a skin rash after sun exposure), leukopenia (defined as <4,000 white blood cell count on two different occasions), thrombocytopenia (defined as <100,000 platelets on a blood count analysis), hemolytic anemia (defined as having anemia associated with positive Coombs test and evidence of hemolysis), pleural effusion (defined as having a positive chest x-ray with evidence of pleural effusion), pericardial effusion (defined as having a positive echocardiogram with pericardial fluid), microhematuria (defined as having persistently >5 red blood cells on urinalysis), proteinuria (defined as having >500 mg proteinuria on a 24 hour urine collection), migraine headaches (defined as having a diagnosis of migraine headaches by a physician), convulsions (defined as having at least one episode of convulsion not related to metabolic disorders, or trauma), psychosis (defined as having in the past the diagnosis of a psychotic behavior), antidsDNA antibody (defined as a positive test on record analysis), and abortions (defined as to ever had one episode or more of a fetal dimise).

Vascular events were arterial thrombosis (defined as to ever had a thrombotic event on an artery including peripheral arteries and cerebrovascular events) or venous thrombosis (defined as ever having a thrombotic event on the venous system including deep vein thrombosis and pulmonary emboli).

Anticardiolipin antibodies included were IgG and IgM antiphospholipids. The titers were considered positive for IgG if >20 MPL U/ml and for IgM if >11 by enzyme-linked immunoabsorbent assay (ELISA) technique.

A detailed interview was done and the information was collected in a data sheet.

The data sheet included a questionnaire inquiring about the family history of RP, history of systemic illnesses, smoking, migraines, abortions, and thrombosis. The SLE clinical manifestations and systems involved were recorded. Thrombotic events including arterial thrombosis, venous thrombosis, amputation of a digit or extremity, and spontaneous abortion were recorded. The medical chart was also used to verify data, obtain the clinical manifestations, obtain laboratory information as the presence of antids DNA and proteinura, and to confirm relevant data.

After the interview, the subject was subjected to a physical examination of the extremities and the skin. A test for ACL Abs type IgG and IgM by ELISA was done.

The tests were done in the rheumatology laboratory of the University of Puerto Rico School of Medicine. The laboratory measured the presence of ACL by enzyme-linked immunosorbent assay (ELISA) using the SIGMA Diagnostics SIA Anticardiolipin test kit. The results were considered positive for IgG antibodies if greater than 20 GPL units/ ml, and for IgM antibodies if greater than 11 MPL units/ml.

Descriptive statistics for continuous variables including mean and standard deviation were computed. Frequency distributions and percents were used for categorical quantitative variables, as well as box-plots and quantile plots. To determine statistical associations among categorical variables, the Pearson's chi-square test or Fischer's exact test, when appropriate, was used.

To compare continuous variables such as age, years of SLE disease between the four study groups (RP+ ACL+, RP+ ACL-, RP- ACL+, RP- ACL-), the analysis of variances (ANOVA) or Kruskal Wallis, when appropriate, was used. The polytomous logistic regression was used to estimate the magnitude of the associations among study groups (RP+ ACL+, RP+ ACL-, RP- ACL+, RP- ACL-) and clinical characteristics such as photosensitivity, oral ulcers, leucopenia, migraines, and thrombotic complications with RP- ACL- as the reference group.

The level of significance was $p<0.05$. All statistical tests were two-sided. Data entry was performed using Epi-info 6.04D. The SigmaPlot software was used to plot the graphics.

The STATA package was used to perform the statistical analysis.

Results

236 SLE patients were enrolled in the study. The population consisted of 159 patients (67.2%) from the University Hospital and 77 patients (32.8%) from the private practice.

The RP+, ACL+ group had 41 patients, the RP+, ACL- group had 63 patients, the RP- ACL+ group had 49 patients and the group with RP- ACL- had 82 patients.

The majority of the patients in the study were female 216 (91.6%). RP+ ACL+ had 39, the RP+- ACL- had 57, the RP- ACL+ had 48 and RP- ACL- had 72 female patients.

The mean age was similar among the four groups: 33.5 yrs for RP+ ACL+, 33.6 yrs for RP+ ACL-, 33.8 yrs for RP- ACL+, and 35.9 yrs for RP- ACL-.

Duration of disease was similar for RP+ ACL+ (8.5 yrs), RP+ ACL- (9.3 yrs) and RP- ACL- (9.6 yrs), but was much lower for RP- ACL+ (4.7 years) (Table 1).

The clinical manifestations among the groups studied are shown in table 2. The following clinical manifestations were more prevalent among patients with RP+ and ACL+, when compared to the other three groups: photosensitivity ($p= .001$), oral ulcers ($p=0.035$), and migraine headaches ($p=.002$) (Table 2). When logistic regression was done for these variables it was found that the odds ratio for photosensitivity (OR 4.12) and oral ulcers (OR 4.01) was markedly increase compared to the other three groups taking the group RP- ACL- as our reference group (Table 3). Thus the combine presence of RP and ACL increase the risk of these patients of having more photosensitivity and oral ulcers.

As to migraine headaches both the RP+ ACL+ (OR 5.31)

Table 1. Demographics Characteristics of 263 Patients With Systemic Lupus Erythematosus Divided in the Four Study Groups

	Study Group				
Characteristics	**RP(+) ACL(+) N=41**	**RP(+) ACL(-) n=63**	**RP(-) ACL(+) n=49**	**RP(-) ACL(-)** n=82**	**p-value**
Gender					
Female	39(95.1)	57(90.5)	48(98.0)	72(87.8)	0.120
Male	2(4.9)	6(9.5)	1(2.0)	11(12.2)	
Age	33.5±14.3	33.6±10.6	33.8±14.2	35.9±16.0	0.687
Health care					
government	34(82.9)	43(68.3)	31(63.3)	55(66.3)	0.188
private	7(17.1)	18(36.7)	20(31.7)	28(33.7)	
*Years with SLE disease	7 (0-23)	8 (0-33)	3 (0-17)	7 (0-36)	0.21
Smoking	3(7.3)	8(12.7)	2(4.1)	7(8.4)	0.434
Hypertension	11(26.8)	23(36.5)	14(28.6)	26(31.3)	0.719
Diabetes mellitus	0(0.0)	3(4.8)	5(10.2)	9(10.9)	0.109

*Median (min-max)
**Reference group

Table 2. Clinical Manifestations of the Four Studied Groups

Clinical Manifestations	Study Group				
	RP(+) ACL(+) n=41	RP(+) ACL(-) n=63	RP(-) ACL(+) n=49	RP(-) ACL(-)** n=82	p-value
Arthralgia/arthritis	35(85.4)	61(96.8)	42(85.7)	74(90.2)	0.149
Malar rash	28(68.3)	39(61.9)	31(63.3)	49(59.8)	0.832
Discoid rash	4(9.8)	4(6.3)	2(4.1)	3(3.7)	0.520
Oral ulcers	7(17.1)	6(9.5)	4(8.2)	4(4.9)	0.035
Photosensitivity	22(53.7)	33(52.4)	13(26.5)	18(22.0)	.001
Leukopenia	14(34.1)	24(38.1)	7(14.3)	19(23.2)	0.023
Thrombocytopenia	4(9.8)	14(22.2)	6(12.2)	12(14.6)	0.298
Hemolytic anemia	7(17.1)	13(20.6)	12(24.5)	9(11.0)	0.210
Pleural effusion	5(12.2)	3(4.8)	5(10.2)	10(12.2)	0.454
Pericardial effusion	1(2.4)	2(3.2)	0(0.0)	2(2.4)	0.767
Microhematuria	6(14.6)	14(22.2)	12(24.5)	17(20.7)	0.700
Proteinuria	14(34.1)	25(39.7)	18(36.7)	38(46.3)	0.541
Migraine headaches	12(29.3)	16(25.4)	6(12.2)	6(7.2)	.002
Convulsions	3(7.3)	7(11.1)	3(6.1)	6(7.3)	0.770
Psychosis	4(9.8)	6(9.5)	4(8.2)	10(12.2)	0.892
antisDNA	19(70.4)	23(60.5)	22(78.6)	26(63.4)	0.424
Abortions	6(15.4)	11(18.3)	10(22.2)	12(17.4)	0.868

**Reference group

Table 3. Association Between the Study Groups and the Clinical Manifestations by Logistic Regression

Study Group	OR	Photosensitivity 95 % CI[o]	p-value
RP(+) ACL(+)	4.12	(1.84, 9.22)	0.001
RP(+) ACL(-)	1.28	(0.56, 2.92)	0.551
RP(-) ACL(+)	3.91	(1.90, 8.03)	1.44
**RP(-) ACL(-)	1.00	-	-
Study Group	**OR**	**Oral ulcers 95% CI[o]**	**p-value**
RP(+) ACL(+)	4.01	(1.10, 14.63)	0.035
RP(+) ACL(-)	1.73	(0.41, 7.27)	0.452
RP(-) ACL(+)	2.05	(0.55, 7.61)	0.282
**RP(-) ACL(-)	1.00	-	-
Study Group	**OR**	**Migraine headaches 95% CI[o]**	**p-value**
RP(+) ACL(+)	5.31	(1.82, 15.47)	0.002
RP(+) ACL(-)	1.79	(0.54, 5.89)	0.338
RP(-) ACL(+)	4.37	(1.60, 11.94)	0.004
**RP(-) ACL(-)	1.00	-	-

[o] 95 % Confidence Interval
** Reference group

and RP- ACL+ (OR 4.37) groups have an increase relative risk (Table 3), thus it could be attributed to the presence of the ACL antibody. More severe manifestations of SLE such as thrombocytopenia, hemolytic anemia, convulsions, and history of proteinuria did not differ among the four groups.

Even when abortions in SLE patients are associated with the presence of anticardiolipin antibodies, the prevalence of abortions was similar among the four groups (Table 2).

Arterial vascular thrombosis was more frequent in the group that had RP and ACL (RP+ACL+) positive, although it was not statistically significant (P=.094). But when polytomous logistic regression was used to estimate the association between the four study groups, there was an increase in relative risk for group RP+ ACL+ (odds ratio 3.21) compared to the RP- ACL- group used as reference group (Table 5).

There was a tendency toward an increased venous thrombosis in the group that was RP+ ACL+, but it did not reach statistical significance (P=.07). When relative risk was studied it was found increased in the group RP+ ACL+ (odds ratio 3.11) compared to the reference group RP- ACL- (Table 5).

Table 4. Vascular Events Among the Four Studied Groups

	Study Group				
Vascular events	**RP(+) ACL(+) n=41**	**RP(+) ACL(-)**	**RP(-) ACL(+) n=49**	**RP(-) ACL(-) n=63**	**p-value "n=83**
Arterial thrombosis	7(17.1)	3(4.8)	3(6.1)	5(6.0)	0.094
Venous thrombosis	8(19.5)	3(4.8)	6(12.2)	6(7.2)	0.067

"Reference group

Table 5. Relative Risk for Arterial and Venous Thrombosis Among the Four Study groups Using Logistic Regression

Study Group	**Arterial Thrombosis**			**Venous Thrombosis**		
	OR	**95 CIØ**	**p-value**	**OR**	**95 CI**	**p-value**
RP(+) ACL(+)	3.21	(0.95, 10.84)	0.060	3.11	(1.00, 9.67)	0.050
RP(+) ACL(-)	1.02	(0.23, 4.46)	0.094	1.79	(0.54, 5.89)	0.338
RP(-) ACL(+)	0.78	(0.18, 3.39)	0.741	0.64	(0.15, 2.67)	0.542
RP(-) ACL(-)"	**1.00**	-	-	**1.00**	-	-

" Reference group
Ø 95% Confidential interval

Discussion

In this study we tried to establish if having both the presence of RP and ACL may confer an increase risk of arterial or venous thrombosis episodes. We found that there were more cases of arterial and venous thrombosis in the group that has both Raynaud's (RP+) and anticardiolipin antibodies (ACL+).

These patients had an increase in relative risk for both arterial thrombosis and venous thrombosis when compared to our reference group RP- ACL- . This suggests that both the presence of Raynaud's phenomenon and anticardiolipin antibodies in a lupus patient may predispose to arterial and venous thrombosis. It was expected to see more arterial and venous thrombosis in the groups that had ACL+, both the RP+ ACL+ and RP- ACL+. The group that had only ACL+ (RP- ACL+) had a lower relative risk for arterial and venous thrombosis than the reference group (RP- ACL-) (see table 4); suggesting that it was the combination of both factors the presence of RP and ACL that increase the risk for thrombosis for both arterial and venous thrombosis in our population.

The association between ACL and thrombosis both arterial and venous have been documented in many articles in the literature in patients with SLE (6, 15, 16, 17, 18, 19, 20), and in patients without SLE or other collagen diseases (21, 23). It is also believed that in patients with ACL the presence of another coagulation abnormality or prothrombotic risk factor increases furtherly the risk of thrombosis (23). It has not been studied if RP may act as a cofactor in these patients with ACL to furtherly increase this risk. Several authors have studied if there is a relationship between the presence of RP and the presence of ACL antibodies in patients with SLE and without SLE, but the results have been conflicting (10,11,12). In the study by Vayssairat et al. (10) it was found that the prevalence of abnormal ACL was higher in patients with RP than in patients with collagen disease or control subjects. The study by Caccavo et al. (11) found no association between ACL antibodies and RP in SLE. Hudson et al (23) did not find neither an association between the presence of ACL and RP.

In our study the four groups have similar percentages of abortions. The number of abortions were not increased in the groups that were ACL+. The presence of anticardiolipin antibodies have been associated with abortions in patients with SLE. In the literature many studies have described one or more fetal loss in 13-68% of those patients with both SLE and ACL+ (6), and in 10-20% of women with ACL but without SLE (6,7). The absence of higher numbers of abortions in our groups with ACL+ could be due to the fact that the test was not done at the moment of the abortion.

Migraine headaches were found more frequently in the patients that had both RP and ACL positive (RP+ ACL+) and in the group that had RP- and ACL+. When logistic regression analysis was done it was found that patients in the RP+ ACL+ and RP- ACL+ group had higher relative risks than the other two groups. Thus, the presence of the ACL antibody seems to increase the probability of the patients with ACL+ of having 4-5 times more headaches than those with ACL-. Headache is a very common symptom among patients with SLE (up to 70% report headaches). Active disease, the presence of anticardiolipin antibodies and presence of Raynaud's phenomenon have been linked to migraine headaches (24,25). Weder-

Cisneros et al (24) also showed that RP may be a risk factor for headaches in SLE patients.

In this study the presence of photosensitivity and oral ulcers were more frequent in patients with RP. Several studies (2,26) have found that the presence of RP correlates with the presence of milder SLE disease, particularly limited to skin and musculoskeletal manifestations. Three studies in patients with SLE have attempted to correlate clinical severity of disease with RP. Lavras et al (26) demonstrated a higher risk of skin lesions and myopathy, and lower risk of nephritis and nephrotic syndrome in patients with RP.

Dimant et al (2) demonstrated that RP in patients with SLE was associated with a milder disease.

Our study had many limitations. It was a cross-sectional study. In a prospective study maybe more episodes of thrombotic events would have been observed. The levels of anticardiolipin antibodies were measured at the moment of the interview, they were not measured at the moment of the abortions or thrombotic events, thus some negative results at the moment of the test may not reveal a past presence of these circulating antibodies, as ACL levels fluctuate over time (15). Lupus anticoagulant was not measured, which sometimes correlates more with venous thrombosis episodes (15).

The levels of cholesterol values, the cumulative dose of steroids and the use of medications such as aspirin, hydroxychloroquine or heparin were not recorded. Although it was thought that the level of ACL may change with corticosteroid use, several studies have not found a difference in these levels between treated and untreated patients (6).

The importance of this study is that patients with SLE that have both Raynaud's phenomenon and the presence of a positive anticardiolipin antibodies seem to be at a higher risk for venous thrombotic events. These patients need to be identified as they may benefit from therapies like hydroxychloroquine or low dose aspirin to prevent these episodes.

Resumen

Introducción: El fenomeno de raynaud (FR) y los anticuerpos contra las cardiolipinas (ACL) son dos manifestaciones clínicas comunes en los pacientes con lupus eritematoso sistémico (LES). El FR puede llevar a perdida digital o de una extremidad. Las ACL se asocian con episodios trombóticos. Todavía no esta claro si hay asociación entre el FR y la presencia de ACL en los pacientes de LES.

Objetivo: Estudiar si la presencia de ambos FR y ACL en pacientes de LES puede asociarse con ciertas manifestaciones o eventos trombóticos comparado a los pacientes de LES que no tienen FR o ACL.

Metodos: Pacientes de LES se obtuvieron de dos clínicas de lupus. Los pacientes se dividieron en 4 grupos. Pacientes con FR y ACL positivo (FR+ ACL+), pacientes con FR pero sin ACL (FR+ ACL-), pacientes que no tenían FR pero si tenían ACL (FR- ACL+), y pacientes que eran negativos para ambos FR y ACL (FR- ACL-) estos se usaron como el grupo control. Data demografica, criterios diagnósticos, manifestaciones clínicas, historial de trombosis venosa y arterial, e historia de abortos se recolectaron. Se hizo un historial fisico. ACL de tipo IgG e IgM se midieron. Estadística descriptiva, analisis de variantes, y analisis de regresión logistica se utilizaron.

Resultados: 236 pacientes con LES se estudiaron. Hubo una tendencia de aumento en trombosis arterial (valor de p= 0.094) y de trombosis venosa (valor de p= 0.067) en el grupo que era positivo para ambos PR y ACL (PR+ ACL+). Aunque no fue estadisticamente significativo, cuando se utilizó regresión logistica , ambas trombosis arterial y venosa tenian un aumento de riesgo relativo de 3.21 para arterial y 3.11 para venosa. Manifestaciones clínicas de LES no diferentes entre los cuatro grupos.

Conclusiones: Pacientes con ambos PR y ACL parecen tener un aumento para trombosis arterial y venosa.

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References

1. Edberg J, Salmon J, Kimberly R. Systemic lupus erythematosus. In: Klippel J, Dieppe P, editors. Rheumatology. Philadelphia, PA: Mosby; 1998. p. 7 2.1- 7 2.12.
2. Dimant J, Ginzler E, Schlesinger M, Sterba G, Diamond H, Kaplan D, Weiner M. The clinical significance of Raynaud's phenomenon in systemic lupus erythematosus. Arthritis Rheum 1979; 22: 815-9.
3. Freedman RR, Mayes M. Familial Aggregation of Primary Raynaud's Disease. Arthritis Rheum 1996 Jul; 39: 1189-91.
4. Klippel J. Raynaud's Phenomenon. Primer on the Rheumatic Diseases,11th edition. Atlanta: Arthritis Foundation; 1997. p.268.
5. Turton EP. The etiology of Raynaud's phenomenon. Cardiovascular Surgery 1998 Oct; 6: 431-40.
6. Love P, Santoro S. Antiphospholipid Antibodies: Anticardiolipin and the Lupus Anticoagulant in Systemic Lupus Erythematosus (SLE) and in Non-SLE Disorders. Annals of Internal Medicine 1990; 112: 682-698.
7. Levine S, Branch D W, Rauch J. The Antiphospholipid Syndrome. N Engl J Med 2002;346:752-763.
8. Naldi L, Locati F, Marchesi L, Cortelazzo S, Finazzi G, Galli M,

et al. Cutaneous manifestations associated with antiphospholipid antibodies in patients with suspected primary antiphospholipid syndrome: a case-control study. Ann Rheum Dis 1993; 52: 219-222.

9. Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps M, Jacobsen S et al. Antiphospholipid Syndrome. Clinical and Immunologic Manifestations and Patterns of Disease Expression in a Cohort of 1,000 Patients. Arthritis & Rheumatism 2002 April; 46: 1019-1027.
10. Vayssairat M, Abuaf N, Baudot N, Deschamps A, Gaitz J.. Abnormal IgG cardiolipin antibody titers in patients with Raynaud's Phenomenon and/or related disorders: prevalence and clinical significance. J Am Acad Dermatol 1998;38: 555-8.
11. Caccavo D, Del Porto F, Garcia P, Mitterhofer A, Galluzzo S, Rigon A, et al. Raynaud's phenomenon and antiphospholipid antibodies in systemic lupus erythematosus: is there a association? Ann Rheum Dis 2003; 62: 1003-5.
12. Bongard O, Bounameaux H, Miescher P, De Moerloose P. Association of anticardiolipin Antibodies and abnormal nailfold capillaroscopy in patients with systemic lupus erythematosus. Lupus 1995; 4: 142-4.
13. Hochberg M. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997; 40: 1725.
14. Wigley F, Flavahan N. Scleroderma. Rheum Dis Clin North Am 1996; 22: 765-81.
15. Somers E, Magdar L, Petri M. Antiphospholipid antibodies and incidente of venous Thrombosis in a cohort of patients with systemic lupus. J Rheumatology 2002;29:2531-6.
16. Wahl DG, Guillemin F, de Maistre E, Perret C, Lecompte T, Thibaut G. Risk for venous thrombosis related to antiphospholipid antibodies in systemic lupus erythematosus: A meta-analysis. Lupus 1997; 6: 467-73.
17. Ginsburg KS, Liang MH, Newcomer L, Goldhaber S, Schur P, Hennekens C et al. Anticardiolipin antibodies and the risk for ischemic stroke and venous thrombosis. Ann Intern Med 1992; 117: 998-1002.
18. Petri M. The Hopkins lupus cohort: a longitunidal study of predictors of thrombosis. Lupus 1994; 3:361.
19. Shah NM, Khamashta MA, Atsumi T, Hughes GRV. Outcome of patients with anticardiolipin antibodies: a 10 year follow-up of 52 patients. Lupus 1998; 7:3-6.
20. Verro P, Levine SR, Tietjen GE. Cerebrovascular ischemic events with high positive anticardiolipin antibodies. Stroke 1998; 29 (11): 2245-53.
21. Oger E, Leroyer C, Dueyones M, Le Moigne E, Bressolette L, Escoffre M, et al. Association between IgM anticardiolipin antibodies and deep venous thrombosis in patients without systemic lupus erythematosus. Lupus 1997; 6: 455-61.
22. Wahl DG, Guillemin F, de Maistre E, Perret-Guillaume C, Lecompte T, Thibaut G. Meta analisis of the risk of venous trombosis in individuals with antiphospholipid antibodies without underlying autoimmune disease or previous thrombosis. Lupus 1998; 7:15-22.
23. Hudson M, Herr AL, Rauch J, Neville C, Chang E, Ibrahim R, et al. The presence of multiple prothrombotic risk factors is associated with a higher risk of thrombosis in individual with anticardiolipin antibodies. J Rheumatol 2003; 30: 2385-91.
24. Weder-Cisneros ND, Tellez-Zenteno JF, Cardiel MH, Guibert Toledano M, Cabiedes J, Velazquez-Paz AL, et al. Prevalence and factors associated with headache in patients with systemic lupus erythematosus. Cephalia 2004; 24: 1031-44.
25. Appenzeller S, Costallat LT. Clinical implications of migraine in systemic lupus erythematosus: relation to cumulative organ damage. Cephalia 2004; 24: 1020-30.
26. Lavras Costallat LT, Valente Coimbra AM. Raynaud's phenomenon in systemic lupus Erythematosus. Rev Rhum Engl Ed 1995; 62: 349-53.