DISTRIBUTION AND CLINICAL SIGNIFICANCE OF LUPUS ANTICOAGULANT AND ANTICARDIOLIPIN ANTIBODY WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Abstract

There is strong association of lupus anticoagulant (LAC) and anticardiolipin antibody (ACA) with systemic lupus erythematosus (SLE) and clinical events like thrombosis, neuropsychiatric manifestations, pregnancy loss and thrombocytopenia. The study was designed to determine the frequency of LAC and ACA in patients with SLE and to determine the relationship of LAC and ACA with the clinical manifestations in SLE patients. This prospective, observational study was done in department of medicine of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, during the period from July 2000 to April 2001. Consecutive 45 patients who attended the lupus clinic and fulfilled the 1982 revised criteria for SLE of the American Rheumatism Association (ARA) were enrolled. All patients were female. Age range of the patients was 16 to 52 years with mean age of 26.6 years. LAC positivity was found in 40 %, and 62 % were positive for ACA. Features of thrombosis was present in 67% of LAC positive patients, while in 7% of LAC negative patients (P<0.001). History of and present neuropsychiatric manifestations were found in 39 % of LAC positive and in 18% of LAC negative patients. History of pregnancy loss were found in 38 % in LAC positive instead 3 % in LAC negative group (P<0.05). History of thrombocytopenia was found in 11 and 7 % respectively in LAC positive and negative group. We have estimated IgG and IgM isotype of ACA, frequency of which were 44.5 % and 53 %, respectively. Features of thrombosis were present in 45% of IgG positive patients and in 20 % of IgG negative patients (P>0.10). Other features like history of and present neuropsychiatric manifestations were present in 40 vs 12 %, history of pregnancy loss in 25 vs 12 %, history of thrombocytopenia in 10 vs 8 %, of IgG ACA positive and negative groups, respectively. Features of thrombosis in IgM positive group were 33 % while in 28 % of IgM negative group (P>0.50). Other features were found not significantly associated. Approximately half of the patients with SLE were found to be associated with one or more or both antibodies. History of thrombosis, neuropsychiatric manifestations, pregnancy loss, and thrombocytopenia were associated LAC and ACA positive SLE patients, though in some respect significant associations were not found.

Keywords: systemic lupus erythematosus; lupus anticoagulant; anticardiolipin antibody; thrombosis; neuropsychiatric manifestations; pregnancy loss and thrombocytopenia

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Introduction

The lupus anticoagulant (LAC) and anticardiolipin antibody (ACA) overlapping subsets of antiphospholipid (aPL) antibodies, were originally described in systemic lupus erythematosus (SLE)[1-4]. Subsequently these antibodies were found in other rheumatological disorders[5,6,7], acquired immunodeficiency syndrome[8], syphilis[9], patients with recurrent abortion or intrauterine foetal death, normal healthy person, and in association with administration of drug chlorpromazine, procainamide etc[10-12]. The activity of LAC correlates with the presence and potency of various ACA [13, 14], a group that include IgG, IgM, IgA. In all probability, most but not all LAC are ACA[15,16].

However, it has been recently shown that anticoagulant activity and anticardiolipin activity can be separated physically[17, 18]. LAC and ACA are strongly associated with diverse set of venous and arterial thromboses, recurrent fetal wastage, neuropsychiatric disorder and thrombocytopenia which together comprises the aPL syndrome[19-21]. Difference in the method used to detect aPL antibodies have contributed to wide range of reported frequencies. Moreover, assay for LAC defer considerably in sensitivity and assay of ACA vary respecting the antibody class or classes and cutoff level of positivity. Recently, standardized methods for assay of ACA have been introduced [22, 23].

Patients with LAC have been more or less successfully treated with steroid, low dose aspirin, antiplatelet agents, warfarin, heparin, etc. Better understanding of the pathogenesis of clinical manifestations of SLE with aPL antibodies (LAC and ACA), and more standardization of the methods of detection, outcome of treatment and wellbeing of the patients have also been improving during the last decade. So therefore, this study has been designed to find out the frequency of LAC and ACA in patients with SLE and to determine the relationship of LAC and ACA with the clinical manifestations in SLE patients.

Materials and methods

A prospective, observational study in which consecutive 45 patients attended in the lupus clinic in BSMMU, Dhaka, for the period from July 2000 to April 2001 and fulfilling the 1982 revised criteria for SLE[24] of American Rheumatism Association were enrolled. Informed consent has been taken from all of them. All 45 patients were interviewed in detail and reviewed past records with special attention to: a) History or clinical manifestations of thrombosis, b) History of or present neuropsychiatric manifestations, c) Past obstetric history, d) History of thrombocytopenia, e) Drug history. The relevant findings and parameters were recorded in pre designed data collection sheet. Data collected on pre designed questionnaire for each individual case was compiled on a master chart and data entered into computer for statistical analysis using computer based software (InStat). Fisher's exact test has been used to determine the significance.

Results

All patients were female. Age range of the patients is 16 to 52 years with mean age of 26.6 years.

Evidence of clinical features such as thrombosis, neuropsychiatric manifestations, foetal loss, thrombocytopenia were evaluated by their records since the time of diagnosis of SLE and are shown in Table I.

Table I: Clinical and laboratory findings in patients with SLE (n= 45)

Presentation	Number of patients	Percentage
History of features of thrombosis	14	31.4
History and present neuropsychiatric manifestations	11	24.4
History of pregnancy loss	7	15.5
History of thrombocytopenia	4	6.6

For the detection of LAC, we have done activated partial thromboplastin time (APTT) and dilute Russel's viper venom time (dRVVT). Any one of them prolonged was considered positive for LAC. APTT was prolonged (37 seconds of more) in 13.3% (6/45) and dRVVT was prolonged (patient- control ratio > 1.05) in 26.6% (12/45). Any one of them prolonged, either APTT or dRVTT, were considered LAC positive. Overall 40% (18/45) were positive for LAC and 62 % (28/45) were positive for IgG and/or IgM ACA(Table- II). The percentage of LAC positivity in ACA positive cases were found to be 42% (12/28), while out of 18 LAC positive cases, 16 patients(88 %) were found to be positive for ACA (IgG and IgM).

Table II: LAC and ACA positivity in SLE patients(n = 45)

Presentation	Number of patients	Percentage
LAC positive	18	40
IgG ACA positive	20	44.5
IgM ACA positive	24	53.0
Both IgG Plus IgM positive	16	33.3
IgG or IgM, any one positive	28	62.0

Features of thrombosis was present in 12 of 18 LAC positive patients (67%), and in 2 of 27 LAC negative patients (7%), which was highly significant (P<0.001). History of and present neuropsychiatric manifestations were found in 39%(7/18) of LAC positive and in 18%(5/27) of LAC negative patients (not significant). History of pregnancy loss were found 38 % (7/18) in LAC positive instead 3 % (1/27) in LAC negative group (P<0.05). History of thrombocytopenia was found in 11 % and 7 %

respectively in LAC positive and negative group (non significant) Table III.

Table III: Comparison between LAC positive and LAC negative patients with clinical manifestations of SLE

Parameters	LAC^{+ve} (n = 18)	LAC^{-ve} (n = 27)	P Value
History or features of thrombosis	12 (66.6%)	2 (7.1%)	< 0.001
History of and present neuropsychiatric manifestations	7 (38.8%)	5(18.2%)	$>0.10^{NS}$
History of pregnancy loss	7 (38.8%)	1(3.7%)	< 0.05
History of thrombocytopenia	2 (11.1%)	2(7.4%)	$>0.10^{NS}$

IgG and IgM isotype of anticardiolipin antibody was studied and found positive in 44.5 % (20/45) and 53 % (24/45), respectively. Features of thrombosis were present in 45 % (9/20) of IgG positive patients while 20 % (5/25) in IgG negative patients (P>0.10). Other features like history of and present neuropsychiatric manifestations were present in 40 vs 16 %, history of pregnancy loss in 25 vs 12 %, history of thrombocytopenia in 10 vs 8 %, in ACA IgG positive and negative groups, respectively (not significant) Table- IV. Features of thrombosis in IgM positive group were 33 % while 28 % in IgM negative group (P>0.50) Table- IV. Other features were also found not significantly associated. We also compared either IgG or IgM positivity (28 patients out of 45) with the clinical findings in patients with SLE and found no significant association (Table V).

When we compared both LAC and ACA positive to both negative patients, we found frequency of thrombosis is 44.4 vs 10.5 percent (P < 0.05). History of and present neuropsychiatric manifestations, history of pregnancy loss and thrombocytopenia showed no significant association (Table- VI).

Discussion

The significance of aPL antibody, e.g. LAC and ACA with SLE has been recently reviewed. In the present study, a total number of consecutive 45 patients with SLE were analyzed. We found the frequency of LAC positive patients with SLE was 40 %. Reports of the prevalence of LAC with SLE patients vary from 5 to 73 % [27-29] . In a large review by Love and Santaro[25, 26] comprising over 1000 patients showed an average prevalence of LAC with SLE was 34%. Angles-Cano et al. studied 28 patients and found 43% of their patients were LAC positive[30]. Harries at al. studied on 59 patients with SLE and found frequency of LAC positivity in 49%[31]. Our finding is more or less consistent to those other reported estimates. On the other hand, the frequency of ACA found in our study was 62%. Here, IgG and/or IgM positive for ACA were considered ACA positive. Reported frequencies of ACA positive varied from 21 to 63% 27, 28, 32 with an average of 42%. Weidmann et al. worked on 92 SLE patients and found 58% of their patients were positive for ACA[33]. Derkson et al[34] studied 111 SLE patients and found that ACA positive cases were 57%. Our estimate is also compatible with above observations, but higher than reported average. This may be due to specificity of the methods used to detect ACA or study on a different population.

Recent studies have shown a close relationship between the presence of LAC and elevated ACA Level[28,35]. We found 42% of ACA positive patients had LAC activities, and on the other hand, 88 % of the LAC positive patients were IgG or IgM ACA positive. Ninomiya et al[36] found the percentage of LAC positive patients with ACA as 60%, while LAC detected in 46.3% of patients with ACA, i.e. half of the patients with LAC or ACA had both antibodies. Our observations showed about half of the ACA patients have LAC activity while more than two-third of the LAC positive patients was ACA positive. In fact LAC and ACA are the overlapping subsets of aPL antibodies and can react with same or closely related epitopes of anionic phospholipids.

Several clinical features, such as thrombosis, neuropsychiatric manifestations, foetal loss and thrombocytopenia were found to have significant association with LAC and ACA positivity in patients with SLE[24,36]. Frequency of thrombosis in LAC positive groups was 67 % than those of 7 % in LAC negative group, which was statistically significant (P<0.001). Carreras et al. found 68 % of their patients with SLE with LAC positivity had history of thrombosis[37]. Boey et al. have shown 58 % of their patients with SLE were LAC positive with thrombosis[38]. In another large review, accumulated data showed that thrombotic events occurred in 42 % of LAC positive patients[26]. Our finding showed higher incidence of thrombosis than accumulated average but closely agree with the findings of Carreras et al.[37"] and Boey et al[38].

Table IV: Clinical and laboratory findings of IgG ACA and IgM ACA positive SLE patients

Parameters	IgG ACA^{+ve} (n = 20)	IgG ACA^{-ve} (n = 25)	P value (n = 24)	IgM ACA^{+ve} (n = 21)	IgM ACA^{-ve}	P value
History of features of thrombosis	9 (45.0%)	5 (20.0%)	> 0.10 ^{NS}	8 (33.0%)	6 (28.0%)	> 0.50^{NS}
History and present neuropsychiatric manifestations	8 (40.0%)	4 (16.0%)	> 0.05 ^{NS}	7 (29.0%)	5 (23.0%)	> 0.50^{NS}
History of pregnancy loss	5 (25.0%)	3 (12.0%)	> 0.10^{NS}	4 (16.0%)	4 (19.0%)	> 0.50^{NS}
History of thrombocytopenia	2 (10.0%)	2 (8.0%)	> 0.50^{NS}	2 (8.0%)	2 (9.5%)	> 0.20^{NS}

Table V: Comparison between IgG or IgM ACA positivism with the clinical and laboratory findings in SLE patients

Parameters	IgG or IgM ACA positive (n = 28)	IgG or IgM ACA negative (n = 17)	P value
History of features of thrombosis	11(39.2%)	3 (17.6%)	>0.10^{NS}
History of and present neuropsychiatry manifestations	10 (35.7%)	2 (11.7%)	>0.10^{NS}
History of pregnancy loss	10 (35.7%)	2 (11.7%)	>0.50^{NS}
History of thrombocytopenia	2 (7.1%)	2 (11.7%)	>0.50^{NS}

Table VI: Comparison between both LAC and ACA positive and negative patients with clinical and laboratory findings of SLE

Parameters	Both LAC & ACA positive (n = 18)	Both LAC & ACA negative (n = 19)	P value
History of features of thrombosis	8 (44.4%)	2 (10.5%)	< 0.05*
History of and present neuropsychiatric manifestations	7 (38.8%)	2 (10.5%)	>0.05^{NS}
History of pregnancy loss	3 (16.6%)	2 (10.5%)	>0.50^{NS}
History of thrombocytopenia	1 (5.5%)	0	>0.10^{NS}

When we compared the frequency of thrombosis with IgG, IgM, IgG and/or IgM positive ACA, we found no significant association though frequencies were higher than antibody negative group. Forty five percent of IgG ACA positive patients had evidence of thrombosis versus 20% of antibody negative (not significant), 33 % of IgM ACA positive versus 28 % antibody negative and 39 % of IgG or IgM positive cases had the evidence of thrombosis versus 18 % of negative patients. But when we compared with double positive group (both ACA and LAC positive) with double negative group, we found significantly higher incidence of thrombosis (P<0.05). Harris et al.[39] found that 58 % of ACA positive patients had the evidence of thrombosis. Petri et al40 found 53 % of ACA positive patients had evidence of thrombosis. Nosima et al. found the higher prevalence of thrombosis in ACA and LAC double positive patients than single positive patients[41]. We considered as the evidence of thrombosis from past and present clinical events, such as skin necrosis, gangrene of the digits, livido reticularis, deep vein thrombosis, etc. We did not go for investigational approach to diagnose thrombosis. So, there may be false positive or false negative results. Moreover, similar clinical findings in diagnosing thrombosis also occur in SLE patients. These may be the reasons for the higher incidence of thrombosis in our series.

The occurrences of neuropsychiatric manifestations in our estimation were found in a frequency of 39% of LAC positive patients to 18% in LAC negative patients (not significant), 40% of IgG positive to 12% of IgG negative (not significant), 29% of IgM positive to 23% of IgM negative (not significant) and 35% of IgG or IgM positive to 12% of negative patients (not significant) respectively. Though no significant associations were found but frequencies were much higher. Neurological disorders documented in our series were psychosis, depressive disorders and seizures. Love and Samuel26 found in combined data analysis that 38% of the LAC positive patients had neurological disorder and 49% of ACA positive patients had neurological disorder. Boey et al38 found that 55% of their patients with LAC had neurological disorder. Manussakis et al. found that 22% of ACA positive patients had neurological disorder [43]. Shergy et al[44]. found that 50% of ACA positive patients had neurological events. Overall incidence of neuropsychiatric manifestations is reasonable in LAC positive group

but lower in ACA positive patients. This may be due to small sample size. Moreover, criteria for diagnosing neuropsychiatric disorders are not still clearly described and psychotic disorders were not critically assessed.

Foetal loss is most interesting phenomenon associated with aPL antibody and it occurs irrespective of associated disease and may occur at any trimester. Thrombosis of placental vessels and placental infarction are thought to be the mechanism of foetal loss[45]. History of foetal loss occurred in our LAC positive patients was 38% and only 3% in LAC negative patients, which was statistically significant ($P < 0.05$). We found no significant association with foetal loss to IgG, IgM, IgG or IgM, or both ACA positive patients, but the frequencies were higher in IgG ACA positive (25 % vs 12%) and IgG or IgM ACA positive (21% vs 12%) to antibody negative groups. Derue and colleagues[45] reported a frequency of 74% of LAC positive patients had one or more spontaneous abortion. Clauvel and colleague[46] reported a frequency of abortion in 50% for LAC positive and 36% of ACA positive patients with SLE. Our observations about foetal loss not up to that range. We studied on consecutive patients. So, patient's selection and referral bias may be the reason for this. Women in this region may have been more reluctant to disclose the information pertaining to previous pregnancy. This may be another reason for the reduced rate of pregnancy loss in our antibody positive patients.

We studied the occurrence of thrombocytonenia associated with LAC and ACA positive patients in SLE, but neither LAC nor ACA positivity were found to be significantly associated with thrombocytopenia. Out of 45 patients with SLE, only 4 had a history of thrombocytopenia. Accumulated data showed[24] that 38% of the LAC positive patients, and 32% of the ACA positive patients had one or more incidence of thrombocytopenia. Platelet membrane sensitivity to aPL antibody may be the likely mechanism. Fewer events of thrombocytopenia in our finding may be due to use of corticosteroid. Moreover, platelet count in our patients were not done in every follow-up visits.

Majority of our patients were taking corticosteroid which has been prescribed by other physicians. Corticosteroid has a suppressive effect on the LAC[2,47,48] and to lesser extent on the ACA[45,48]. This may be the reason why some of our findings were not correlated with other studies on aPL antibodies. Other reasons may be small sample size, different population and consecutive or unselected patients in our study.

Recommendation: a major goal of the future clinical studies will be to evaluate the prognostic usefulness of aPL antibodies. To accomplish this task, long range prospective series will be required. This should include i) a well-characterized but unselected cohort of patients and controls, matched for age ii) early identification of disease iii) proper evaluation of clinical manifestations iv) serial measurement of aPL antibodies v) define criteria for the diagnosis of thrombosis, neurological disorder and vi) documentation of therapy.

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