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General Medicine

PREVALENCE AND SPECTRUM OF CARDIO-VASCULAR DISEASE IN LUPUS PATIENTS AND THEIR TREATMENT OUTCOMES.

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ABSTRACT Systemic lupus erythematosus (SLE) has pleomorphic cardio-vascular manifestations that may remain clinically silent. Our study aims to estimate the prevalence of clinically overt and silent cardiovascular abnormalities in known SLE patients and to describe the spectrum, using trans-thoracic echocardiography. This is an ambi-directional study in which 248 newly diagnosed SLE patients were sampled consecutively over 34 months. In 83 patients, a trans - thoracic ECHO was done at presentation as per clinical requirement. A follow-up ECHO after 6 months of treatment was done when feasible. Abnormalities in ECHO were found in 56 patients, commonest being valvular lesions. These did not correlate with patient's duration of illness, disease activity, antibody status. Follow-up ECHO showed improvement in ECHO parameters with immunosuppressive therapy. Cardiovascular manifestations in SLE may not correlate with clinical presentation, hence a careful clinical scrutiny, followed by an ECHO when needed, will be beneficial.

KEYWORDS : Anti-phospholipid Syndrome, Echocardiogram, Pulmonary Artery Hypertension, Systemic Lupus Erythematosus, Valvular regurgitation

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disorder resulting in multi-systemic inflammatory damage. Its cardio-vascular manifestations are pleomorphic and may remain clinically silent [5,3]. Pericardium, myocardium, valves, pulmonary arteries and coronary arteries can be involved in patients with SLE[19].

In recent years, with prolonged survival and improvement in diagnostic techniques,(Trans-thoracic / Trans-oesophageal Echocardiography or other advanced modalities), the cardio-vascular disease associated with SLE has become more apparent & its prevalence is estimated to be 50% [17]. Studies using trans-oesophageal echocardiography (TOE) have shown valvular disease to be the commonest cardiac abnormality (61%) [17], whereas those using trans-thoracic echocardiography have shown pericarditis to be the commonest abnormality[6,14].Cardio-vascular involvement in lupus may or may not be related to the clinical presentation, disease activity or duration of illness [14].

Antiphospholipid antibodies (APLAs) are present in over 20% of lupus patients, and have been strongly associated with cardiac involvement in SLE patients [7,11,12]. APLA positivity has association with thrombosis, valvular thickening, valvular endocarditis, and coronary artery disease.

Our study aims to estimate the prevalence of clinically overt and silent cardiovascular abnormalities in known SLE patients and to describe the spectrum, using trans-thoracic echocardiography. We also aim to determine any relation with clinical features, disease activity, duration of illness, antibody status. Outcome of patients with cardiovascular abnormalities on immunosuppressive therapy is studied by clinical follow-up and ECHO follow-up study.

MATERIALS AND METHODS

STUDY POPULATION

This is an ambi-directional study, done from January 2015 - January 2018, on newly diagnosed SLE patients fulfilling the EULAR/ACR criteria 2012 presenting to a tertiary care hospital (St John's Medical College and hospital, Bengaluru, India). A total of 248 SLE patients (inpatient or outpatient) were sampled consecutively over a period of 34 months.

INCLUSION CRITERIA

1. Newly diagnosed SLE patient - fulfilling the EULAR/ACR criteria 2012 - Inpatient or Outpatient in SJMCH, Bengaluru

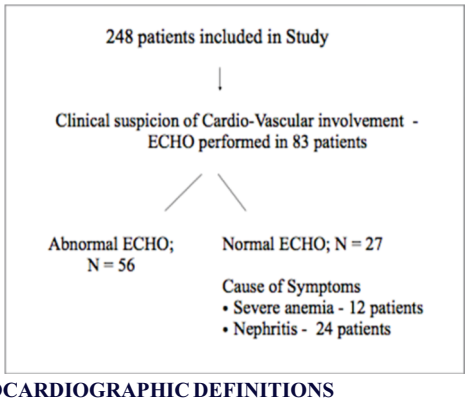
EXCLUSION CRITERIA

1. Age < 18 years or > 60 years
2. Known Ischemic/Rheumatic heart disease on treatment
3. Not consenting for study

STUDY PROTOCOL

Of the 248 patients who were sampled, eighty three patients had symptoms and signs suggestive of Cardio-vascular illness; in them a trans - thoracic ECHO was done at presentation. If this ECHO had abnormal findings, it was followed- up by a repeat trans- thoracic ECHO after at-least 6 months of immunosuppressive treatment.

Details of illness including SLEDAI score, comorbidities were noted and routine laboratory evaluation was done, at presentation and at all follow-up visits (once a month for first 3 months, once in 3 months subsequently). All patients were treated with steroids and immunosuppressants as per clinical requirement.



ECHOCARDIOGRAPHIC DEFINITIONS

Semiquantitative sizing of pericardial effusion was done by measuring the rim of fluid between the epicardium and parietal pericardium at end-diastole [15]. The size cutoffs taken were - Small - <10mm, Medium - 10 to 20mm and Large - >20mm. Left ventricular hypertrophy was

measured as left ventricular wall thickness of >12 mm in diastole. Left and right ventricular internal dimensions were measured in diastole and dilatation was reported if these were >58 mm and >20 mm respectively [15]. Valve thickness was measured from the parasternal long axis view and valvular thickening was reported if the maximum thickness was 3 mm or more [15]. Regurgitation, jet volume and velocity were assessed and severity was graded for all 4 valves. Pulmonary artery pressure was calculated from the tricuspid regurgitation jet and pulmonary hypertension was diagnosed if this was > 40 mmHg [15,18], studies have shown that patients with PASP > 40mm Hg have higher mortality [18].

STATISTICAL ANALYSIS

Descriptive statistics were reported using mean and standard deviation for the continuous variables, number and percentages for the categorical variables. Chi-square test was used to test the association between categorical variables, Independent t test was used to compare the mean between two groups else Mann Whitney U test was used. P value less than 5% was considered as statistically significant. All the analysis was carried out using SPSS version 23.0.

ETHICS CLEARANCE

Institute Ethics Committee clearance was obtained for the study. There was no external funding for this study. There was no conflict of interest.

RESULTS

BASELINE CHARACTERISTICS OF STUDY POPULATION (AT PRESENTATION)

The mean age of study population is 29.18 ± 11.07 years, with a Female : Male ratio of 86 : 14. The mean duration of illness (in months) at the time of diagnosis is 2.13 ± 1.72. Most patients had muco - cutaneous and musculoskeletal complaints at presentation, 67% and 59% respectively. Forty-six percent patients had active nephritis and 23% patients had neuropsychiatric manifestations at presentation. Anaemia (Hb < 10 mg/dl) and hypertension (BP >140/90 mm Hg) were present in 38 (45.7%) and 17 (23%) patients respectively. Mean SLEDAI score of study population at presentation (i.e. at the time of first ECHO study) was 12.28 ± 3.61.

APL antibody levels (anti - Cardiolipin and Lupus anticoagulant) were available in 69/83 patients, of which, 27 were positive. Four patients had APLA syndrome (past poor obstetric outcome in 3, thrombotic events in 3). Table 1 gives the baseline characteristics of study population.

CLINICAL PRESENTATION OF PATIENTS IN WHOM CARDIO-VASCULAR INVOLVEMENT WAS SUSPECTED

Patients suspected to have cardio-vascular disease at presentation underwent a Trans-thoracic Echocardiogram. Table 2 gives the indication for performing ECHO in study

Table 2 - Indication for performing ECHO in Study Subjects (N=83).

Indication (at Presentation)	Number of Subjects
Breathlessness	20
Chest Pain	14
Pedal Edema	29
Hypertension	19
Hypotension / Shock	2
Fatigue	24
Cough	12
Systolic Murmur in Apex	13

*42 patients had more than 2 symptoms/signs.

subjects.

ECHOCARDIOGRAPHIC FINDINGS

Fifty-six patients were found to have abnormal ECHOs. The commonest abnormality noted in our study population was Valvular disease in 39 (47%) patients. The most valve abnormality was regurgitation, observed in 39 patients. Pattern of involvement of valves in descending order: tricuspid (84%) > mitral (72%) > aortic (38.5%) > pulmonary (7.2%). Combined valvular regurgitation was seen in 19 subjects.

Valvular vegetations i.e. Libman Sachs endocarditis were noted in 4 subjects, all four were APS positive. Valvular vegetations were most commonly seen involving anterior and posterior mitral leaflets, ranging in size from 0.5mm to 12mm. Aortic vegetations were not seen in our patients.

Table 3 : Types of Doppler - Echocardiographic abnormalities (at the time of presentation) in Study population (N=83).

Lesion	Number (%)
Pericardial Abnormality	
Mild effusion	18 (21.7)
Moderate effusion	1 (1.2)
Severe effusion	0
Left Ventricular Dysfunction	
Global hypokinesia	6 (7.2)
Regional hypokinesia	0
Diastolic dysfunction	23 (27.7)
LV Hypertrophy	4 (4.8)
Valvular Lesion	
Endocarditis - Vegetation	6 (7.2)
Regurgitation	39 (46.9)
Right heart dysfunction	
Pulmonary Artery Hypertension (>40mm Hg)	27 (32.5%)

ECHO Indice	Number of Subjects (%)
Ejection Fraction < 50%	7 (8.4)
Enlarged LA (diameter > 38mm)	17 (20.4)
PASP > 40 mm Hg	27 (32.5)

Pulmonary artery hypertension (PASP > 40 mm Hg) in 27 (32.5%) patients. However, it was noted that 66 (79%) patients had PASP > 25mm Hg. Pericardial effusion was seen in 19 patients, however, none of them had cardiac tamponade.

CORRELATION OF ECHOCARDIOGRAPHIC FINDINGS (AT PRESENTATION) WITH CLINICAL FEATURES

Among the 83 patients who were suspected to have cardio-vascular disease, twenty-seven were found to have a normal ECHO; 12 had severe anemia (Hb<7g/dl) and 24 were found have severe renal disease.

Among the 56 patients with abnormal ECHO study, six patients had LV global dysfunction and were all symptomatic. The symptoms that correlated well with presence of abnormal findings on ECHO were breathlessness and pedal edema (p=0.025 and 0.002, respectively). Two patients who presented with Hypotension/Shock had Severe LV dysfunction.

Presence of anaemia, hypertension, nephritis, neuropsychiatric SLE did not correlate with patient having an abnormal ECHO. The SLEDAI score or severity of SLE at presentation or duration of illness at presentation did not correlate with the presence of abnormal ECHO findings

Table 4 - Correlation studies between the ECHO abnormalities and the duration of illness and SLEDAI Score.

Lesion	Duration of Illness (>3 months since onset of symptoms)	SLEDAI Score (>12)
Pericardial Abnormality	0.14	0.11
Left Ventricular Dysfunction	0.21	0.17
Valvular Lesion		
Endocarditis - Vegetation	0.07	0.06
Regurgitation	0.10	0.08
Pulmonary Artery Hypertension (>40mm Hg)	0.45	0.35

* Significant p < 0.05

Patients with anti-phospholipid antibody positivity were found to have more abnormalities in ECHO (increased valvular regurgitation and PAH) as opposed to those who were anti-phospholipid antibody negative

Table 5 : Prevalence of ECHO abnormalities among Anti-phospholipid antibody positive and negative patients (N=57).

Lesion	APS Positive N = 21 (%)	APS Negative N = 26 (%)	P Value
Pericardial Abnormality	5 (23.8)	10 (38.4)	0.08
Left Ventricular Dysfunction			
Global hypokinesia	1 (4.7)	2 (7.6)	0.65
Regional hypokinesia	3 (14.2)	2 (7.6)	0.4
Diastolic dysfunction	7 (33.3)	12 (46)	0.87
LV Hypertrophy	1 (4.7)	2 (7.6)	0.87

Valvular Lesion			
Endocarditis - Vegetation	4 (19)	0 (0)	**0.002**
Regurgitation	15 (71.4)	16 (61)	0.06
Right heart dysfunction Pulmonary Artery Hypertension (>40mm Hg)	9 (42.8)	6 (23)	**0.03**

*Antiphospholipid antibody status unknown in rest.

(p=0.002).

TREATMENT DETAILS

All patients received steroids and immunosuppressants as warranted clinically. Patients with renal, neuropsychiatric and hematologic manifestations were treated with IV pulse steroids followed by standard dose oral steroids. The median (IQR) dose of oral steroids initiated was 40 (IQR - 20 to 50) mg/day.

Ninety-five percent patients were started on Hydroxy-chloroquine, Cyclophosphamide and Mycophenolate mofetil was started in 19% and 23% respectively. Methotrexate and Azathioprine were initiated in 32 patients each.

Patients with Pulmonary artery hypertension (PASP >40 mm Hg) were additionally started on Phosphodiesterase inhibitors and/or Endothelin antagonists as indicated. Patients with myocardial dysfunction were started on beta-blockers, ACE inhibitors, anti-platelets, statins as indicated.

FOLLOW-UP OF STUDY SUBJECTS

Out of 83 study subjects, five expired on follow-up (1 following a CVA, 1 during a nephritis flare, reasons unknown in 3 - lost to follow-up). There was no cardio-vascular event requiring hospitalisation in the remaining 78 patients till last follow-up.

Amongst the 56 subjects with abnormal ECHO at presentation, follow-up ECHO after at-least 6 months of immunosuppressive therapy was possible in 20. In 13 subjects, the abnormalities seen in first ECHO had reversed and become normal.

Table 6: Echocardiographic findings of Follow-up patients (N=20).

Lesion	Initial ECHO Number (%)	Follow up ECHO Number (%)	P Value
Pericardial Abnormality	5 (25)	**0**	**0.01**
Left Ventricular Dysfunction			
Global hypokinesia	2 (10)	**1 (5)**	0.06
Regional hypokinesia	2 (10)	**0**	0.06
Diastolic dysfunction	9 (45)	**0**	**0.01**
LV Hypertrophy	1 (5)	**0**	0.15
Valvular Lesion			
Endocarditis - Vegetation	1 (5)	**1 (5)**	0.07
Regurgitation	11 (55)	**6 (30)**	**0.00**
Pulmonary Artery Hypertension (> 40mm Hg)	9 (45)	**4 (20)**	**0.03**

ECHO Indice	Number of Subjects
Ejection Fraction < 50%	1
Enlarged LA (diameter > 38mm)	2
PASP > 40 mm Hg	4

DISCUSSION

Our study showed a female preponderance of SLE with age of disease onset consistent with earlier literature [1,21]. The prevalence of renal, neuropsychiatric SLE, hematologic, musculoskeletal, cutaneous involvement was similar to rates reported by Ahmad et al and Tucker et al. The mean SLEDAI score at presentation of our patients is high, this probably reflects the fact that sicker patients maybe presenting to our centre which is a tertiary referral centre. A median delay of 2 months between symptom onset and initiation of treatment is decent compared to other studies[1,3].

Prevalence and Types of Cardiac abnormalities

We found a high prevalence of Echocardiographic abnormalities (68.6%) in our patients. Valvular disease was the most common finding, with tricuspid followed by mitral regurgitation being the most prevalent, similar to reports by Nikdoust et al [13]. Western studies show predominant mitral and aortic valve disease [3,21], there are no Indian studies to compare the above. No stenotic lesions were noted.

Unlike the series reported by Galve et al, we had no patients with valve thickening or stiffness. This maybe due to age and racial differences as suggested by Crozier et al [4]. Pericardial effusion was observed in 19 patients, however only one had clinically significant effusion.

Almost 32.5% had significant pulmonary artery hypertension similar to other studies in South-Asian population [10,13], though studies in Caucasian subjects report lower prevalence [9,19]. There is a possibility of overestimation of pulmonary pressures by trans-thoracic ECHO as opposed to the gold standard - right heart catheterisation [8]. Other contributing factors like presence of underlying lung disease, chronic thromboembolism, renal disease etc need to be studied further [16].

Correlation of SLE disease activity with cardiac disease Our study did not find a correlation between prevalence of cardio-vascular disease and disease severity or duration of illness. Several studies over the years have demonstrated the same [5,6,14].

APS and Cardiac disease -

Several studies on patients with Primary APS and SLE - APS have reported abnormalities include valve thickening, regurgitation, Libman Sacks endocarditis, rarely stenosis [7,11,12]. In our study, the proportions of valvular regurgitation and PAH were higher among APL positive patients, than in APL negative patients, however the differences were statistically not significant. All four patients with Libman-Sacks endocarditis were anti-phospholipid antibody positive.

FOLLOW-UP OF PATIENTS

There was no significant difference in the clinical outcome of patients with abnormal ECHO findings and higher initial SLEDAI score or longer duration of disease. Since repeat ECHO was not feasible in all 83 patients due to financial constraints or refusal, we are unable to comment on specific cardio-vascular outcomes.

LIMITATIONS OF OUR STUDY

Some limitations of our study include ECHO being performed by more than one operator, lack of confirmation of Pulmonary pressures with the gold standard - Right heart catheterisation. Also, Antiphospholipid antibody levels were not available in all patients and traditional risk factors of cardio-vascular disease were not studied.

CONCLUSION

- Detection of Cardiovascular manifestations in SLE requires careful clinical scrutiny, followed by an ECHO when needed.
- Early identification of patients with significant valvular regurgitation, thickening or pulmonary hypertension and prompt institution of appropriate immunosuppressive therapy may reduce overall morbidity.
- Patients should also be evaluated for traditional risk factors of cardio-vascular disease like diabetes mellitus, hypertension, dyslipidemia and managed accordingly.

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