Point Prevalence of Cardiac Abnormalities in Children with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To determine the point prevalence and pattern of silent cardiac abnormalities and associations with suspected risk factors in a sample of children with systemic lupus erythematosus (SLE).

Methods. Cross-sectional analysis of 19 children with SLE from a referral-based rheumatology clinic at an urban children's hospital. Patients were eligible if they were 20 years of age or younger and classified with SLE using the revised criteria of the American College of Rheumatology. Each patient completed a survey, physical examination, standard 12-lead electrocardiogram (ECG), echocardiogram, and had laboratory determinations of complement, triglyceride, and cholesterol levels.

Results. Six patients (32%) had cardiac abnormalities on ECG or echocardiogram. In 3, the abnormalities were mild and considered within the normal range. In 5, the abnormalities were considered silent. These abnormalities included ischemic changes (3 patients), valvular insufficiency (3 patients), ventricular repolarization defects (2 patients), cardiac enlargement (1 patient), and ventricular dysfunction (1 patient). Only a recent history of palpitations was significantly associated with the presence of cardiac abnormalities ($p = 0.04$).

Conclusions. Silent cardiac abnormalities can occur in children with SLE. A recent history of palpitations may be associated with cardiac abnormalities. Routine evaluation of children with SLE using ECG and echocardiogram may help screen for these abnormalities. However, future studies comprising larger sample sizes and longitudinal followup will be required to determine the natural history of cardiac abnormalities in children with SLE and to identify risk factors. (J Rheumatology 2001;28:854–9)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS HEART DISEASES PEDIATRICS

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disorder that may affect virtually every organ system in the body. It is a relatively uncommon condition, with prevalence estimates of up to 31 per 100,000 children under 15 years of age[1]. Despite substantial improvements in the survival and quality of life of children with SLE, morbidity due to SLE continues to be a major cause of concern[1,2]. Renal disease, central nervous system (CNS) disease, and infection have historically been considered the major causes of morbidity and mortality in pediatric SLE[1-7]. Cardiac disease is now being recognized as a significant cause of morbidity and mortality in children with SLE[2,8].

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The spectrum of cardiac disease in children with SLE mirrors that in adults with SLE and encompasses 4 major types[8]: pericarditis[9,10], myocarditis[9,11], valvular disease[12,13], and coronary artery disease due to either coronary arteritis[13–15] or atherosclerosis[11,14,16]. In mainly adult studies of SLE, duration of SLE[17-19], antiphospholipid antibodies[18,20-25], anti-Ro and anti-La antibodies[9,26], renal disease[22], glucocorticoid use[19,22], and hypercholesterolemia[19] have been associated with cardiac disease[27-31]. Little is known about associated risk factors for cardiac disease in children with SLE.

There are few published reports of cardiac disease in children with SLE to date. Little is known regarding the prevalence and pattern of cardiac disease in an outpatient panel of children with SLE in whom cardiac disease is not suspected[11]. Using noninvasive screening tests, we determined the point prevalence and pattern of cardiac abnormalities in a sample of children with SLE without regard to past history of heart disease. In addition, we explored associations between cardiac abnormalities found on screening evaluation and suspected risk factors.

MATERIALS AND METHODS

All children with SLE followed in the Rheumatology and Nephrology clinics at the Children's Hospital of Philadelphia and the Children's Seashore House between January 1 and March 31, 1990, were eligible for

enrollment in our study. All patients were recruited for enrollment by mail, telephone, and personal solicitation during clinic visits or hospitalizations during this time period. Patients were not recruited on the basis of prior heart disease but were eligible for inclusion if they were 20 years of age or younger, had onset of disease by age 16, and were classified with SLE by the revised criteria of the American College of Rheumatology (ACR) for the diagnosis of SLE[32]. Patients were excluded if they had a history of rheumatic heart disease, infective endocarditis, or congenital heart disease. The study protocol was approved by the institutional review board at the Children's Hospital of Philadelphia.

Immediately following enrollment and informed consent, patients completed a survey administered by one of the study investigators. Item content on the survey included questions regarding demographics, established coronary heart disease risk factors, symptoms of heart disease, and sequelae of SLE. Outpatient charts were reviewed to determine mean daily glucocorticoid dosage, cumulative dosage, and duration of use. Patients then underwent a physical examination and had blood drawn for determination of complement (C3), triglyceride, and total cholesterol levels following an overnight fast. The systemic lupus activity measure (SLAM), a clinical and laboratory index of concurrent SLE activity and severity, was determined for each patient on the day of enrollment. The SLAM index reports a single continuous scale that reflects disease activity and severity over the previous 30 days. The SLAM index has been shown to have excellent psychometric properties and correlates well with physicians' impressions of disease activity[33].

To evaluate for cardiac disease, all patients underwent on the day of enrollment, a standard 12-lead electrocardiogram (ECG) and an M-mode, 2D, and color-flow Doppler echocardiographic study. Echocardiograms were performed according to the convention of the American Society of Echocardiography[34] using a Hewlett-Packard echocardiographic machine. ECG and echocardiograms were interpreted by a cardiology fellow and confirmed by a staff cardiologist experienced in such interpretation, both of whom were blinded to study objectives and patient histories except for the diagnosis of SLE. Cardiac abnormalities on ECG were determined according to standard criteria using age-dependent standards[35]. Cardiac abnormalities on echocardiogram were interpreted according to standard accepted criteria. Pericardial effusions were considered present if fluid was detected in the pericardial space on M-mode and 2-D imaging. Cardiac dimensions were measured by M-mode and 2-D images and compared with standard values by weight. Left ventricular function was measured using M-mode imaging to calculate the left ventricular shortening fraction (LVSF) (normal range: 28-44%). Valvular stenosis was considered present if increased transvalvular pressure gradients were present and color reversal at the site of peak velocity occurred. Valvular regurgitation was considered present if a regurgitant jet was visualized by color flow imaging using multi-angled views and was graded as trace, mild, moderate, or severe. Trace or mild regurgitation without cardiac symptomatology was deemed normal.

Cardiac abnormalities determined by ECG or echocardiogram at the time of enrollment represented the main outcome variable. Cardiac abnormalities were considered silent if there was no past history of significant heart disease (excluding acute pericarditis) and there were no symptoms or signs at enrollment suggestive of current heart disease. Demographic variables, known cardiac risk factors, possible cardiac symptoms, and SLE sequelae were assessed for their association with cardiac abnormalities. These factors were selected for analysis *a priori* on the basis of known or suspected association with heart disease in a general pediatric population and in adults with SLE. Fisher's exact test was used to assess the statistical significance of associations involving dichotomous variables, and the Students' t test was used to assess the statistical significance of associations involving continuous variables. An association was deemed statistically significant if a corresponding p value of < 0.05 was obtained. No adjustment for multiple comparisons was made due to the small sample size. Statistical analysis was performed using STATA statistical software (College Station, TX), version 5.0.

RESULTS

We identified 35 children who were classified with SLE from clinic enrollment files, but we were only able to contact 27 to solicit participation. Of these, 19 (70.4%) enrolled and completed the study. None met criteria for exclusion. There were 15 females (79%) and 4 males (21%). The mean age was 15.0 years (range 8 to 20). With respect to race, 10 were white, 7 were black, 1 was Hispanic, and 1 was Asian. These patients were seen consecutively and not on the basis of cardiac symptoms or prior heart disease.

Six patients (32%) had abnormalities on ECG and/or echocardiogram suggestive of cardiac disease (Table 1). The pattern of these abnormalities included ventricular depolarization defects (2 patients), Q-wave abnormalities (2 patients), mild to moderate valvular regurgitation (3 patients), ventricular repolarization defects (2 patients), cardiac enlargement (1 patient), and ventricular dysfunction (1 patient). No patient had evidence of pericarditis. Five of the 6 patients were considered to have silent cardiac abnormalities (except Patient 16).

Associations between cardiac abnormalities and demographic characteristics, SLE activity and complications were evaluated (Table 2). The mean SLAM index for all study patients was 7.8 (reference range 0-20), indicating moderate disease activity. Nine patients had lupus nephritis and were followed jointly in the nephrology clinic. Seventeen patients had a history of arthritis, although only 9 had active arthritis at the time of enrollment. Ten patients had active cutaneous vasculitis at the time of enrollment, and 4 had a history of CNS disease including 1 who had a cerebrovascular accident. Patients with cardiac abnormalities were not significantly different from those without cardiac abnormalities with respect to age, race, sex, duration of SLE, mean SLAM index, active arthritis, active renal disease, active vasculitis, or history of CNS disease. There was a trend among patients with cardiac abnormalities toward white race and shorter disease duration.

Associations between cardiac abnormalities and established cardiac risk factors or symptoms suggestive of heart disease were evaluated next (Table 3). Overall, 2 patients had insulin-dependent diabetes mellitus, 8 had hypertension and were under treatment, and 6 were current smokers. Patients with cardiac abnormalities were not significantly different from those without cardiac abnormalities with respect to symptoms of exercise intolerance or exertional chest pain, insulin-dependent diabetes mellitus, hypertension, and current smoking status. Patients with cardiac abnormalities were significantly more likely to report a history of recent palpitations ($p = 0.04$).

Laboratory indices and glucocorticoid usage were evaluated for association with cardiac abnormalities (Table 4). With regard to laboratory indices, 5 patients (26.3%) had laboratory evidence of elevated cholesterol or triglyceride levels. Eight patients (44.4%) had low complement C3

Table 1. Distribution of cardiac abnormalities.

Patient	Age (yrs)	Sex	ECG Result	Echocardiogram Result
1	11	F	NSR	NEC
2	16	F	NSR	NEC
3	14	M	NSR	NEC
4	9	F	NSR	Pulmonic Regurgitation, mild Tricuspid Regurgitation, mild
5	16	F	NSR	Mitral Regurgitation, mild
6	17	F	NSR/RAD of 110°	NEC
7	19	F	NSR	NEC
8	15	F	NSR	NEC
9	13	M	NSR/AQW of 5 mm in lead III	NEC
10	8	F	NSR	NEC
11	15	F	NSR	NEC
12	16	F	NSR	NEC
13	19	M	NSR	NEC
14	17	F	NSR	NEC
15	17	F	NSR	NEC
16	15	M	NSR/LAD of +10° AQWs 6 mm in III & aVF; 3 mm in V6 QTc of 0.44 seconds	Mitral Regurgitation, moderate Dilated left ventricle LVSF of 15%
17	15	F	NSR/QTc of 0.46 seconds	NEC
18	13	F	NSR	NEC
19	20	F	NSR	NEC

NSR: normal sinus rhythm; NEC: normal echocardiogram; RAD: right axis deviation; AQW: abnormal Q-wave; LAD: left axis deviation; LVSF: left ventricular shortening fraction.

Table 2. Demographic and disease characteristics in children with and without cardiac abnormalities.

Variable (mean ± SD)	Cardiac Abnormality N = 6 (%)	No Cardiac Abnormality N = 13 (%)	p*
Age (yrs)	14.2 ± 2.9	15.4 ± 3.4	0.45
Race			0.14
White	5 (83.3)	5 (38.5)	
Black	1 (16.7)	6 (46.1)	
Asian	0	1 (7.7)	
Hispanic	0	1 (7.7)	
Female (%)	4 (66.7)	11 (84.6)	0.55
Duration of SLE, yrs	2.2 ± 1.2	4.1 ± 3.5	0.09
SLAM indices	7.2 ± 4.0	8.2 ± 5.6	0.70
Active arthritis (%)	3 (50.0)	6 (46.2)	1.00
History of CNS disease (%)	1 (16.7)	3 (23.1)	1.00
Active renal disease (%)	2 (33.3)	7 (53.9)	0.63
Active vasculitis (%)	2 (33.3)	8 (66.7)	0.32

*Differences between 2 groups assessed by Student's t-test for continuous variables or Fisher's exact test for categorical variables.

levels (below 0.80 g/l). With regard to glucocorticoid usage, the mean daily steroid dose was 0.52 mg/kg/day (range 0.19 to 1.75), the mean cumulative duration of steroids was 819 days (range 225 to 2665), and the mean cumulative steroid dose was 363 mg/kg (range 75 to 1194) for all patients.

Table 3. Cardiac symptoms and coronary heart disease risk factors in children with and without cardiac abnormalities.

Variable	Cardiac Abnormality* N = 6 (%)	No Cardiac Abnormality* N = 13 (%)	p**
Exercise intolerance	1 (16.7)	6 (46.2)	0.33
Exertional chest pain	4 (66.7)	7 (53.9)	0.66
Palpitations	4 (80)	2 (18.2)	0.04
Insulin dependent diabetes mellitus	0 (0)	2 (15.4)	0.54
Hypertension	3 (50)	5 (38.5)	1.00
Current smoking	2 (33.3)	4 (30.8)	1.00

*Expressed as absolute number with percent of total responding to a given question in parentheses.
**Differences between 2 groups assessed by Fisher's exact test.

Patients with cardiac abnormalities were not significantly different from those without cardiac abnormalities with respect to concurrent laboratory values of total cholesterol, triglycerides, and C-3 complement levels. Nor were patients with cardiac abnormalities significantly different from those without cardiac abnormalities with respect to glucocorticoid usage: total duration of steroid use, total steroid dose, and mean daily dose of steroids. Patients with cardiac abnormalities tended to have a shorter duration of steroid use and a lower cumulative steroid dose.

Table 4. Laboratory values and glucocorticoid usage in children with and without cardiac abnormalities.

Variable (mean ± SD)	Cardiac Abnormality N = 6	No Cardiac Abnormality N = 13	p*
Cholesterol (mmol/l)	4.90 ± 1.17	5.05 ± 1.00	0.79
Triglyceride (mmol/l)	5.95 ± 2.60	4.73 ± 2.43	0.35
C-3 (g/l)	0.98 ± 0.49	0.92 ± 0.56	0.82
Duration of glucocorticoid use (days)	461.0 ± 593.1	930.0 ± 806.5	0.23
Cumulative glucocorticoid dose (mg)	190.2 ± 236.9	419.4 ± 389.7	0.21
Mean daily glucocorticoid dose (mg/kg)	0.60 ± 0.62	0.44 ± 0.19	0.42

*Differences between the 2 groups were assessed by Student's t-test for continuous variables and Fisher's exact test for categorical variables.

DISCUSSION

In our study of 19 children with SLE, we found a point prevalence of cardiac abnormalities on ECG or echocardiogram of 32%. Three patients had mild abnormalities that may be within the normal range and may not represent heart disease. Five of the 6 patients had silent cardiac abnormalities. This finding is consistent with published prevalence figures from other centers. In those studies, up to 42% of children with SLE had cardiac abnormalities[3-7,9]. The pattern of cardiac abnormalities in our study included valvular insufficiency, ventricular depolarization and repolarization defects, cardiac enlargement, and ventricular dysfunction.

Five patients (26%) had a history of heart disease at least one year prior to enrollment. One patient (Patient 16) had a myocardial infarction one year prior to the study and still exhibited abnormalities on screening examination. He reported symptoms at enrollment of dyspnea on exertion and exertional chest pain. He was not significantly different from other children with SLE with regard to demographic characteristics; SLE activity, duration, and sequela; steroid usage; and most established cardiac risk factors. He did, however, have serum cholesterol and triglyceride levels that were markedly higher than the mean for the other children with SLE (cholesterol 6.39 mmol/l vs 5.00 mmol/l and triglycerides 6.80 mmol/l vs 5.16 mmol/l). The other patients (Patients 2,5,8, and 14) had a history of acute pericarditis that resolved and was no longer evident on echocardiographic examination. One of these 4 (Patient 5) had evidence of mitral regurgitation on echocardiogram at the time of enrollment that was not present on earlier examination. These children were not statistically significantly different from the other children with SLE with regard to factors examined in the study.

It is unclear from the literature whether children with SLE have silent cardiac abnormalities. In the only published study that addressed this question, Gazarian and colleagues examined children with SLE for myocardial perfusion abnormalities[11]. They found no cardiac symptoms in the 5 patients with perfusion abnormalities suggesting silent abnormalities. We found that 5 of 6 patients with cardiac abnormalities were unsuspected. The only variable significantly associated with the presence of cardiac abnormalities was a recent history of palpitations. Four of 5 patients with cardiac abnormalities (one patient did not respond to this question on the survey) had a recent history of palpitations. This finding was not related to any specific cardiac abnormality, and further research is needed to determine whether this finding is a marker for cardiac disease.

The natural history of cardiac abnormalities in children with SLE is unknown, and we were unable to address this question. It is unknown whether silent cardiac abnormalities progress to clinically symptomatic abnormalities. To date, there have been no published longitudinal studies of heart disease in children with SLE. Roldan, *et al* in a study of adults with SLE found that valvular abnormalities frequently resolved, appeared for the first time, or changed in appearance in a 5 year followup[29]. We were unable to determine any significant associations with clinical and laboratory markers of SLE activity and severity that might identify risk factors for persistent abnormalities.

Although we did not find a significant association with glucocorticoid usage, we observed a trend toward shorter disease duration, shorter time taking steroids, and lower cumulative steroid doses among those with cardiac abnormalities. Two recent studies involving children with SLE noted a similar trend: a retrospective echocardiographic study of children with SLE[9] and a concurrent myocardial perfusion study of children with SLE[11]. In the former study, investigators reported that 42% of children with SLE had cardiac disease; most of those with cardiac disease were identified within 6 months of SLE diagnosis. In the latter study, 5 of 31 patients had segmental perfusion abnormalities, and the investigators noted a non-significant trend toward shorter disease duration and time taking steroids. The implications of these reported trends lend support to the hypothesis that cardiac disease in children with SLE may be a result of poorly controlled disease activity[11]. This would suggest a protective role for glucocorticoids and perhaps other immunosuppressive agents in the development of

cardiac disease. It should be noted, however, that none of these studies were prospective or showed differences in clinical disease activity measures. Adult prospective studies have not shown this same trend[29,40].

Our study has several strengths. First, we used commonly employed screening tests, ECG and echocardiography, to evaluate an outpatient panel of children with SLE for heart disease. ECG and echocardiography are techniques commonly employed in the diagnosis of ventricular hypertrophy, conduction disturbances, dysrhythmias, anatomic abnormalities particularly valvular disease, and ventricular dysfunction. Due to their noninvasive properties, they perform well as screening tools in the initial assessment of patients with suspected heart disease. Second, we attempted to prospectively enroll all children with SLE without regard to past history of heart disease[38]. This allowed us to examine children for silent or unsuspected cardiac abnormalities. Most previous studies in children have consisted of case studies or series that only evaluated symptomatic children and were therefore unable to evaluate for silent abnormalities.

Several limitations of the present study exist. First, the study sample size was small and from a single institution only. Therefore, we may not have had the statistical power to adequately examine important clinical associations. Second, we were unable to adequately evaluate for silent ischemic heart disease. ECG and echocardiography lack sensitivity in the diagnosis of ischemic heart disease, but otherwise are excellent non-invasive screening tests for other forms of heart disease. Had we used a more sensitive but invasive test for myocardial perfusion abnormalities such as thallium scintigraphy, the prevalence of silent abnormalities may have been higher. Third, we did not examine antiphospholipid antibodies in study patients. These were not routinely done at the time of the study, but subsequently have been associated with cardiac abnormalities in children with SLE in other studies. Fourth, we did not include a control population of children without SLE. However, since children without SLE are not expected to have silent cardiac abnormalities, we felt that any abnormalities could be attributed to SLE or its treatment. Fifth, 46% of identified children did not participate in the study. It is possible that those who participated are substantially different from non-participants with regard to cardiac disease and associated factors. Pilot data obtained from five non-participants and clinic enrollment files showed that there were no differences between participants and non-participants with respect to gender, race, and the proportion currently receiving glucocorticoids (80% vs 95%) or other immunosuppressive medications (40% vs 42%). However, non-participants were older (mean 17.0 years vs 15.0), had a longer mean duration of illness (mean 5.2 years vs 3.5), had a higher proportion with arthritis (80% vs. 47%) or hypertension (60% vs. 42%), and had a lower proportion with nephritis (20% vs. 47%) than participants. None of the five non-participants studied either smoked or had diabetes. This suggests that non-participants were older and had a longer duration of disease but were probably similar with respect to disease severity.

We conclude that cardiac abnormalities were common in this outpatient panel of children with SLE. The majority of these abnormalities were silent. In three patients, the abnormalities were mild and may be considered part of the normal range. A history of recent palpitations may be a marker for the presence of these cardiac abnormalities. Future studies comprising larger sample sizes will be required to better determine statistically significant associations with suspected risk factors. Routine screening of children with SLE using ECG and echocardiography may help to diagnose silent cardiac abnormalities; however stress testing and thallium scintigraphy may be better suited to identify silent ischemic defects. Careful follow-up of children with SLE should be employed to assess the natural history of any silent abnormalities discovered.

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