Cardiac abnormalities in children with systemic lupus erythematosus

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SUMMARY: Günal N, Kara N, Akkök N, Çakar N, Kahramanyol Ö, Akalın N. Cardiac abnormalities in children with systemic lupus erythematosus. Turk J Pediatr 2003; 45: 301-305.

Children and adolescents with systemic lupus erythematosus (SLE, n=14) with no cardiac symptoms were examined for cardiac involvement by physical examination, electrocardiography (ECG) and echocardiography. The indexes of left ventricular (LV) systolic and diastolic function were compared with the findings of 20 healthy, age-matched control subjects. Echocardiographic examination revealed mild tricuspid valve regurgitation in three, and moderate tricuspid and mitral valve regurgitation in two patients. Pericardial thickening was found in one patient. Indexes of LV systolic and diastolic function of SLE patients differed significantly from control subjects, with marked reduced ejection fraction (EF) and fractional shortening (FS) as well as reduced peak early diastolic filling velocity (E) and ratio of early-to-late diastolic filling velocity (E/A). Deceleration time (DT) was longer in the patients than in the control group. Late filling velocity (A) and isovolumic relaxation time (IRT) did not differ between the two groups. Valvular and pericardial involvement was found to be lower than previous reports. We conclude that asymptomatic diastolic and systolic dysfunction is common in children with SLE, most likely representing myocardial involvement. Routine cardiac evaluation by echocardiography can be recommended in the follow-up of children with SLE in order to detect silent cardiac abnormalities.

Key words: systemic lupus erythematosus, systolic function, diastolic function, lupus nephritis, echocardiography.

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease. Autoantibody production and complement activation play major roles in the pathogenesis[1]. The most common symptoms are constitutional complaints and joint or skin manifestations. Renal disease and hypertension are also common at the time of presentation. Although SLE is most commonly observed in women aged 20-40, almost 15% of cases have childhood onset, and mild cases in this age group are more frequent than previously recognized[2].

Cardiac involvement in patients with SLE has been described since the early 20th century. The frequency of cardiac manifestations has ranged from 4 to 78% in previous reports[3,4]. Complications may develop in all layers of the heart, including the endocardium, myocardium, pericardium, coronary arteries and the conduction system, although frequently in a subclinical fashion[5].

The purpose of our study is to describe cardiac involvement in children with SLE mainly by echocardiographic evaluation of left ventricular systolic and diastolic functions, and review the literature.

Material and Methods

Fourteen children with SLE diagnosed in our Pediatric Nephrology Clinic between 1993 and 2001 who responded to the invitation of the Pediatric Cardiology Department and 20 healthy sex-and-age matched control subjects were studied. All patients fulfilled the revised criteria of the American College of Rheumatology for the diagnosis of SLE[6]. Data on clinical manifestations and laboratory findings at the time of presentation were obtained from clinical charts. Ten patients underwent kidney biopsies during the follow-up period. For cardiac evaluation, 12-lead electrocardiography (ECG),

telecardiograms and echocardiographic studies were done in all patients. Two dimensional, continuous wave (CW), pulse wave (PW) and color flow Doppler examinations were performed in parasternal and apical views for structural and hemodynamic findings and valvular function. Left ventricular systolic function was determined by measuring the ejection fraction (EF) and fractional shortening (FS) from standard parasternal long-axis view by M-mode echocardiogram. Diastolic function of left ventricle was evaluated by measuring peak early diastolic filling velocity (E), peak late diastolic filling velocity (A), E/A ratio (a measure of relative blood volume, filling the left ventricle in early versus late diastole), isovolumic relaxation time (IRT) (the time between aortic valve closure and mitral valve opening) and deceleration time (DT) (time between peak E to zero point of velocity) by PW Doppler echocardiogram. Valvular function was assessed by CW and color flow Doppler echocardiography. The normal values for peak E and A velocities are 0.73±0.09 and 0.38±0.08 m/sec, normal values for E/A ratio, IRT and DT are 2.0±0.5, 55±10 ms, 199±32 ms, respectively[7]. Echocardiographic studies were performed with Toshiba SSH 160 Sonolayer echocardiograph using 3-5 mHz transducers.

Statistical comparison of SLE and control groups was done using the Independent-Samples t test for normally distributed values, and Mann-Whitney U test for others. Mean values were expressed in mean±SD for t test, and median with minimum and maximum values for Mann-Whitney U test. Statistical significance was assumed at $p<0.05$.

Results

Patients

Female to male ratio was 12/2. Patient's age at the time of the study ranged from 8 to 19 years (mean 13.9±3.6). The average known duration of SLE was 48 (range 8-108) months. Fever, skin rash and arthritis were the major initial complaints. Five patients had signs of central nervous system involvement at presentation: chorea (n=2), hemiparesis (n=1), pseudotumor cerebri and visual loss (n=1) and aseptic meningitis (n=1). Hematologic involvement was present in five patients at the time of diagnosis with hemolytic anemia (n=1), leukopenia (n=1) and thrombocytopenia (n=3). Renal involvement diagnosed by abnormal urinary findings and biopsy was present in 12 patients. All renal biopsy specimens (n=10) showed a wide range of pathologic changes, usually associated with SLE nephropathy. The WHO classification of glomerular lesions were class IV in seven patients, class II-A in one, class II-B in one, and class III-B in one patient[8]. Demographic features and major organ involvement of the patients are shown in Table I and Table II, respectively.

Table I. Demographic Features of Patients with SLE (n=14)

Age (yrs)	13.9±3.7	(8-19)*
Female/male	12/2	
Duration of disease (months)	48.4±33.1	(8-108)*

Mean±1SD.
*(minimum and maximum) values.
SLE: systemic lupus erythematosus.

Table II. Major Organ System Involvement of Patients with SLE (n=14)

Major organ system involvement	Patients	%
Renal	12	86
Cardiovascular	6	43
CNS	5	36
Hematologic	5	36
Skin	4	29
Pulmonary	1	7
Serologic findings (%)		
ANA	11	79
Anti-dsDNA	9	64
ACL	7	50
Hypocomplementemia	14	100

SLE: systemic lupus erythematosus; CNS: central nervous system; ANA: antinuclear antibody; aCL: anticardiolipin antibodies.

All of the 14 patients were normotensive during the study. All had currently inactive disease under treatment with prednisone, dose ranging between 7.5-20 (mean 10) mg/day, and cyclophosphamide 500 mg/BSA once in three months. The duration of prednisone therapy was between 8 and 98 months. Six patients were also taking azathioprine (50-100 mg/day).

Cardiac Findings

Mild systolic murmur was heard at the left sternal border in four patients who had no cardiac abnormality, and innocent murmur was also present in six of 20 control patients. All

telecardiograms were normal. No patient had clinical evidence of cardiac disease, but six of them had abnormalities on ECG and/or echocardiogram suggestive of cardiac disease (Table III). These abnormalities were left axis deviation and ST-T wave changes (ST segment depression and T wave flattening) in three patients. One patient had moderate tricuspid valve insufficiency and one had mitral valve insufficiency detected by CW Doppler echocardiography. Pericardial thickening was detected in one patient. Three patients with SLE and four patients in the control group had mild tricuspid valve regurgitation in the physiologic limits, with early systolic regurgitant velocity less than 2 m/s.

Table III. Distribution of Cardiac Anomalies by Electrocardiography and Echocardiography

	No. of patients	%
ECG findings (LAD, ST-T changes)	3	22
ECHO findings (MR, TR, pericardial thickening)	3	22

ECG: electrocardiopraphy; ECHO: echocardiography; LAD: left axis deviation; MR: mitral valve regurgitation; TR: tricuspid valve regurgitation.

Systolic and Diastolic Function of the Left Ventricle

Although the EF and FS values of the patients were within normal limits (EF: 0.63 and FS: 0.32), they were significantly lower than in normal subjects (EF: 0.68 and FS: 0.38), (p=0.007). EF and FS values were abnormally low in only one patient (EF: 0.53, FS: 0.27). Left ventricular diastolic functions were also impaired with decreased peak E velocity (0.90±0.04 vs. 0.83±0.06, p<0.001), lower E/A ratio (1.91±0.20 vs. 1.75±0.19, p: 0.026) and prolonged DT (144 vs 179, p: 0.001). A wave velocity and IRT values did not differ between the two groups. Table IV summarizes the left ventricular systolic and diastolic parameters of the patients, compared with the control group.

Discussion

Age and sex distributions of our patients were concordant with previous reports[2,9]. The onset of SLE before the age of five years is rare. All our patients were older than seven years, and most (86%) were females. Although the clinical manifestations of SLE in children resemble those in adults, childhood-onset disease is usually associated with more severe organ involvement. Arthritis, arthralgia, malar rash, fever and malaise are the most prominent presenting manifestations of childhood SLE[10,11]. Initial manifestations in children can be atypical at first evaluation, but laboratory abnormalities such as elevated erythrocyte sedimentation rate, anemia and autoantibodies are present in most cases. Kanra et al.[12] reported thrombocytopenia preceding other signs of SLE in a child. Central nervous system disease, parotitis, chorea, persistent cough and generalized lymphadenopathy may be the presenting features of the disease[2,13]. Five patients in our study had neurologic sings as the initial symptom.

The incidence of clinical renal disease as evidenced by proteinuria, hematuria and low glomerular filtration rate was 79% in our patients. All of the renal tissue specimens showed different degrees of glomerular injury. These findings were also consistent with previous reports[14].

Table IV. Left Ventricular Diastolic Filling Parameters and Systolic Functions in Normal Subjects and in Patients with SLE

	No. of patients		
Variables	Normal subjects	SLE	p
E (m/s)	0.90±0.04	0.83±0.06	<0.001
A (m/s)	0.48 (0.38-0.64)	0.46 (0.42-0.58)	0.377
E/A	1.91±0.20	1.75±0.19	0.026
IRT (ms)	72.0 (58-90)	72.0 (64-96)	0.691
DT (ms)	144 (112-184)	189 (112-204)	0.001
EF (%)	67.6±5.0	62.6±4.8	0.007
FS (%)	38 (32-47)	32 (27-40)	0.001

Values are expressed as mean ± 1 SD and (min-max) values; E: peak early filling velocity; A: peak late filling velocity; E/A: ratio of E to A; IRT: isovolumic relaxation time; DT: deceleration time; EF: ejection; FS: fractional shortening; SLE: systemic lupus erythematosus.

Cardiac involvement in SLE was first reported by Libman and Sacks[15] in 1924. Most reports concerning the cardiac findings of SLE concerned adult patients and described various types of abnormalities including endocarditis, myocarditis, valvular regurgitation, pericarditis and conduction disturbances[16-18]. There are limited reports about children with SLE. Guevara et al.[19] found a point prevalence of cardiac abnormalities on ECG or echocardiogram in 32% of 19 children with SLE. This finding is consistent with other studies showing cardiac disease in up to 42% of children with SLE[20]. Smilarly, we found six patients (43%) with cardiac abnormalities on ECG and/or echocardiography. Three patients had ECG abnormalities, with left axis deviation in one and STT wave changes in two patients, including those with moderate tricuspid regurgitation and with systolic dysfunction. ECG findings of these patients were not severe, and none of them had symptoms of apparent heart disease.

Rhythm and conduction disturbances reported in patients with SLE include atrioventricular block, bundle branch block, sinus tachycardia and atrial arrhythmias, and occur in a minority of patients.

Two of our patients, though asymptomatic, had modererate tricuspid and mitral valve insufficiency. Mild tricuspid regurgitation, found in three patients, was considered as a physiological finding unrelated to the disease, as can be seen in the normal population[7].

One patient had diminished systolic function with lower EF and FS values than the normal limits. Although the EF and FS values of the other 13 patients were in normal ranges, a statistically significant difference was found when compared with the control group. This finding may be an early sign of impairment of left ventricular contractile function. A recent five-year prospective study of patients with SLE concluded that abnormalities of systolic and diastolic left ventricular function were common and progressive[21].

Left ventricular diastolic function indexes (peak E velocity and E/A ratio) were decreased and DT was prolonged in the patients. IRT did not differ between the two groups. This impairment of diastolic function was not accompanied by any other clinical manifestation. There were no other causes to affect left ventricular (LV) relaxation in our patients, such as hypertension. The observation of abnormal LV relaxation seen in our patients is an early manifestation of myocardial dysfunction and is in agreement with previous reports[22-24]. Although the pathophysiological mechanism of the diastolic impairment of LV is unclear, immunopathologic changes in myocardium or lupus myocarditis may be responsible for ultimate diastolic dysfunction[25,26]. Clinically apparent cardiomyopathy or myocarditis in SLE is uncommon; most studies have noted a prevalence of about 10%[27].

The treatment of our patients consisted of steroids, azathioprine and cyclophosphamide, although several new treatments for severe refractory cases, such as mycophenolatemofetil and stem cell transplantation, are being increasingly used[28].

Our study has two limitations. First, the relatively small size of the patient group may have prevented the detection of statistically powerful results. Secondly, longer follow-up data, which may provide information on further cardiac involvement or progressive myocardial impairment, are not available yet. Studies with larger sample size will allow a more accurate estimation of the incidence of cardiac involvement, and possible associations with risk factors.

We did not detect serious valvular lesions, endocarditis, pericarditis or conduction disturbances in our patients, but the mild tricuspid valve regurgitation, even if within physiological limits, or minor ECG abnormalities may constitute early sings of cardiac involvement of SLE. Although clinical cardiac abnormalities and findings of structural involvement were not as common in our study is in previous studies, significant differences of systolic and diastolic function between SLE and control patients, even when clinically silent, can be considered as early signs of diastolic relaxation impairment and contractile dysfunction of the left ventricle. Early detection and treatment of cardiac abnormalities in SLE patients may lead to better survival. Therefore, routine cardiac evaluation of children with SLE using ECG and echocardiography is recommended to detect silent cardiac involvement.

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