Cardiovascular complications in paediatric-onset systemic lupus erythematosus in Saudi Arabian patients

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Abstract

Objective

To assess the prevalence and types of cardiovascular complications in Saudi patients with paediatric-onset systemic lupus erythematosus (pSLE).

Methods

Retrospective record review of pSLE patients following from January 2014 to September 2015 at the rheumatology clinic of King Abdul-Aziz University Hospital, Jeddah. Laboratory data such as C-reactive protein (CRP), antinuclear antibodies (ANA), anti-double stranded DNA antibody (anti-dsDNA), C3 and C4 complements, were collected. Cardiac evaluation included chest x-ray, electrocardiogram (ECG), and echocardiography, along with estimation of SLE activity by calculating the SLE Disease Activity Index (SLEDAI) score according to SELENA modification.

Results

Forty-six cases of pSLE were included (91.3% females, mean±SD age at diagnosis=10.53±2.28 years). Prevalence of cardiac manifestations was 47.8%; the most frequent of which were valvular heart diseases diagnosed in 16 (34.8%) cases, followed by pericarditis in 6 (13%) cases. Of the 16 valvular diseases, tricuspid and pulmonary valves were involved in 9 and 8 cases, respectively. Cardiac involvement was silent in 36.4% and occurred as an initial presenting symptom of SLE in 9.1% cases. Biologically, patients with cardiac involvement had higher levels of CRP and anti dsDNA, and lower levels of complement C3 compared to patients with no cardiac involvement; while high SLE activity was the only significant predictor for cardiac involvement (beta=0.654; p=0.020).

Conclusion

Cardiac complications are common in Saudi children with pSLE and are asymptomatic in 1 out of 3 times. They are predicted by high SLE activity and associate with high anti-dsDNA and CRP and low C3 levels.

Key words

systemic lupus erythematosus, paediatric, heart valve diseases, pericarditis, Saudi Arabia

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Introduction

Paediatric-onset systemic lupus erythematosus (pSLE) is an autoimmune disease resulting from dysregulation of inflammatory mediators and immune-response signalling, which leads to systemic vasculitis, immune complex depositions and multi-tissue damage (1-5). Besides immunological disorders, pSLE is suspected and diagnosed by a broad range of manifestations such as malar rash, arthritis, haematologic abnormalities, neurological, and renal disorders. (6, 7). Constitutional symptoms such as fever, lymphadenopathy, and weight loss; as well as other skin manifestations may also be observed (7-9). Epidemiologically, pSLE has low incidence (<1 per 100,000 children-years) and relatively low prevalence of about 3 to 9 per 100,000 children; although higher frequencies are observed in some ethnic groups such as Asians (10-12). More than 1.5 million individuals are affected by SLE in the United States, and 5,000 to 10,000 of them are <18 years (13, 14). Females are more prone to and affected by pSLE similar to most autoimmune disease compared to males. The female to male ratio of pSLE varies from 3:1 to 9:1, as per different studies (15, 16).

In comparison with the adult form, pSLE is marked by higher disease activity, causes greater damage and more impact on the quality of life (6, 15, 17). The evolution of pSLE is marked by frequent complications, especially rapid progression of lupus nephritis into end-stage renal disease (ESRD) and infections, associated with high morbidity and mortality (2, 18, 19). In addition, more neuropsychiatric complications are observed in pSLE by comparison to adult-onset SLE (20).

SLE is a multisystem disease that affects organ systems such as skin, musculoskeletal, renal, lung, gastrointestinal, nervous systems, etc., which translates into a variety of clinical presentations (21). Cardiac involvement among pSLE patients is a known complication considered relatively common. Previous studies reported 25% to 60% of cardiac manifestations in pSLE (7, 22). These manifestations may involve the pericardium, myocardium, endocardium, valves, conduction system, and the coronary arteries (23). Pericarditis was reported to be the most common cardiac abnormality associated with pSLE, followed by myocarditis, valvular disease, and coronary artery disease (24). In some cases, cardiac involvement may be silently present without clinically evident cardiovascular symptoms and is generally detected after extensive investigations (25, 26). Early diagnosis and treatment of pSLE cardiac complications is crucial, as they may carry poor prognosis (7).

The purpose of this work is to study the prevalence of cardiovascular complications of pSLE in the western region of Saudi Arabia. In addition, we wanted to elaborate our understanding regarding the correlations between the risk of developing cardiovascular complications and SLE activity; to enable early detection of high-risk patients and timely management of cardiac complications.

Methods

Retrospective record review of 46 pSLE paediatric patients (16 to 19 years) following for pSLE from January 2014 to September 2015, at the rheumatology clinic of King Abdul-Aziz University Hospital (KAUH), Jeddah. All patients fulfilled the diagnosis criteria of SLE according to the revised American College of Rheumatology (ACR) classification, based on the following criteria: malar rash, discoid rash, photosensitivity, oral ulcers, non-erosive arthritis, pleuritis or pericarditis, renal disorder, neurologic disorder, haematologic disorder, immunologic disorder, and positive antinuclear anti-body. A patient is defined as having SLE if any 4 or more of these criteria are present, serially or simultaneously, during any interval of observation (27). Patients with history of acute rheumatic fever or those with incomplete medical records were excluded. Research Ethics Committee of KAUH approved this study.

Demographic data including age, gender, consanguinity, family history, and presenting manifestations, and laboratory data such as haemoglobin (Hb) levels, weight blood cell counts (WBC) erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear

Table I. Main clinical characteristics of the study population.

		n	Mean	SD
Age at diagnosis of SLE		46	10.53	2.28
Age at cardiac involvement		22	14.00	2.47
			Frequency	Percentage
Gender	Male		4	8.7
	Female		42	91.3
Cardiac complications				
Symptomatic valvular heart disease			8	17.4
Silent valvulardisease			8	17.4
Pericarditis			6	13.0
Total			**22**	**47.8**

Table II. Results of electrocardiogram, chest x-ray and echocardiography.

Investigation / abnormality	Frequency	Percentage
Electrocardiogram		
Low voltage and non-specific QRS complex	6	13.0
Left ventricular hypertrophy	8	17.4
Chest x-ray		
Pleural effusion	4	8.7
Cardiomegaly	12	26.1
Echocardiography		
Tricuspid valve	**12**	**26.1**
Mild regurgitation	8	17.4
Severe regurgitation	4	8.7
Mitral valve	**6**	**13.0**
Severe regurgitation	6	13.0
Aortic valve	**4**	**8.6**
Severe regurgitation	4	8.6
Pulmonary valve	**8**	**17.4**
Mild insufficiency	8	17.4
Pericardium	**6**	**13.00**
Moderate to large pericardial effusion	6	13.00

antibodies (ANA), anti-double stranded DNA antibody (anti-dsDNA), C3 and C4 complement, were collected. In addition, a plain chest x-ray, an electrocardiogram (ECG), and an echocardiography using Vivid E9 (General Electric, New York, USA) were performed for all patients and reviewed by cardiologist.

Subsequently, the SLE Disease Activity Index (SLEDAI) score was calculated for each patient to estimate the activity of the disease at the time of cardiac evaluation according to the SELENA modification (28). These include the past 10 days clinical and laboratory assessments; viz the presence/absence of seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, cerebrovascular accident, vasculitis, arthritis, myositis, urinary casts, haematuria, proteinuria, pyuria, new rash, alopecia, mucosal ulcers, pleurisy, pericarditis, low complement levels, increased DNA binding, fever, thrombocytopenia, and leukopenia.

Laboratory abnormalities were defined as follows: anaemia (Hb <12 g/dL); leukopenia (<3,000 WBC/mm^3); thrombocytopenia (<100,000 platelets/mm^3); elevated ESR >20 mm/hr; elevated CRP >3.0 mg/L; low C3 <0.75 g/L; low C4 <0.2 g/L; ANA strongly positive (1:2800), moderately positive (1:1600) and mild positive (1:32); and anti-dsDNA is high if >30 IU/mL. Abnormal image findings based on reports of the chest x-ray and the electrocardiogram anomalies were also recorded.

The criteria for cardiac involvement were described by echocardiogram findings as follows: pericarditis was defined by the presence of significant pericardial effusion; myocarditis by decreased myocardial function; and valvular heart disease by the disturbance of the blood flow.

Statistical analysis

Descriptive and analytical statistics were conducted on SigmaStat for Windows v. 3.5 (SPSS Inc., San Jose, CA, USA) and SPSS Statistics for Windows, v. 20.0 (Armonk, NY: IBM Corp, 2011). Relative/absolute frequencies were used in the analysis of the qualitative variables, and mean and standard deviation for continuous variables. Comparison between participants with/without cardiac involvement used *t*-test for continuous variables and chi-square test for qualitative variables. Univariate and multivariate binary logistic regression was carried to analyse predictors for cardiac involvement. A p-value <0.05 was considered statistically significant.

Results

Clinical characteristics

The study included 46 children (42 [91.3%] females) of 6 to19 years. The mean (SD) age at SLE diagnoses was 10.53 (2.28) years (Table I). The prevalence of cardiac manifestations was 47.8%, with a mean (SD) age of 14.0 (2.47) years and a mean interval of 3.5 years from the initial SLE diagnosis. Cardiac involvement was symptomatic in 63.6% and silent in 36.4% cases; and occurred as an initial presenting symptom of SLE in 9.1% of cases. The minimum age of cardiac involvement was 10 years (Table I).

Types of cardiac complications

Valvular heart disease was the most frequent cardiac manifestation diagnosed in 16 (34.8%) patients, followed by pericarditis in 6 patients (13%), while no cardiac involvement was detected in the remaining 24 (52.2%) patients. Among valvular heart diseases, (n=16), tricuspid valve was the most frequent involved in 12/16 cases, followed by pulmonary in 8/16 cases, mitral in 6/16, and the aortic valve in 4/16 cases. Valvular involvement was clinically silent in 8/16 cases. The remaining cases of cardiac involvement included pericarditis (6/22). Abnormal cardiac findings diagnosed in ECG, chest x-ray and echocardiography is presented in Table II.

Correlation between laboratory results and cardiac complications

Independent *t*-test was conducted to determine if a difference existed in laboratory results between patients with/without cardiac involvement. Analysis showed that the serum level of anti ds-DNA was higher in patients with cardiac involvement compared to patients without cardiac involvement, with mean level at 1053.80 *versus* 675.80, respectively, (p=0.039). In addition, a significant difference was observed between the 2 groups regarding logarithmically transformed CRP (Ln[CRP]) levels (p=0.042), and complement C3 levels (p=0.012). The activity of SLE as expressed by SLEDAI was significantly increased in patients with cardiac involvement compared to those without (mean SLEDAI score of 19.18 *vs*. 8.13, respectively; p<0.001). Cross-tabulation analysis showed that 22 patients (100%) with cardiac involvement had strongly positive ANA titres, against 66.7% with no cardiac manifestations, (p=0.012). Comparative analysis of laboratory investigations between patients with/without cardiac involvement are summarised in Table III.

Table III. Laboratory data in SLE patients with and without cardiac involvement.

Parameter	Cardiac involvement				
	No (n=24)		Yes (n=22)		p-value
	Mean	SD	Mean	SD	
Haemoglobin (g/dL)	9.95	1.62	9.42	1.43	0.250
WBC count (x10^3/mm^3)	6.68	3.60	7.34	2.14	0.456
ESR (ng/mL)	55.21	31.82	55.59	40.58	0.972
CRP (mg/L)	6.36	5.39	22.08	46.09	0.104
Ln(CRP)	1.64	0.70	2.20	1.16	0.042*
Anti dsDNA (IU/ml)	675.80	482.68	1053.80	707.05	0.039*
Complement C3 (g/dL)	0.802	0.316	0.556	0.316	0.012*
Complement C4 (g/dL)	0.126	0.075	0.104	0.0785	0.341
SLEDAI score	8.13	3.23	19.18	5.55	<0.001*
ANA titre	Freq.	%	Freq.	%	*p*-value
Moderately positive	6	25.0	0	0	0.012**
Positive	2	8.3	0	0	
Strongly positive	16	66.7	22	100	

ANA: antinuclear antibodies; Anti dsDNA: anti-double stranded DNA antibody; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; freq.: frequency; SD: standard deviation; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index SELENA modification; WBC: white blood cells; %: percentage; *statistically significant result (p-value <0.05) using independent *t*-test; **statistically significant result (p-value <0.05) using chi-square test.

Predictors for cardiac involvement

Binomial regression analysis was carried out to determine the predictors for cardiac involvement in pSLE. Anti dsDNA (OR [95%CI] = 1.001 [1.000–1.002]; p=0.046), complement C3 (OR [95%CI] = 0.083 [0.011–0.647]; p=0.017) and SLDEAI score (OR [95%CI] = 1.980 [1.160–3.382]; p<0.001) were significant predictors in univariate regression; however, only the SLEDAI score remained significant in multiple regression model (beta=0.654; p=0.020). ANA titre (strongly positive *vs*. moderately positive) could not be included in the analysis, as the frequency of cardiac involvements was null in the reference category (moderately positive ANA titres) (Table IV).

Table IV. Predictors for cardiac involvement in paediatric-onset systemic lupus erythematosus.

	Univariate regression			Multiple regression		
	OR	95% CI		*p*-value	beta	*p*-value
Age at diagnosis	1.30	0.97	1.75	0.080	-	-
CRP	1.07	0.98	1.17	0.152	-	-
Ln(CRP)	2.13	0.98	4.65	0.057	-	-
ANA	-	-	-	-	-	-
Anti dsDNA (IU/ml)	1.001	1.000	1.002	0.046*	0.001	0.543
Complement C3 (g/dL)	0.083	0.011	0.647	0.017*	-1.604	0.510
SLEDAI score	1.980	1.160	3.382	<0.001*	0.654	0.020*

ANA: antinuclear antibodies; Anti-dsDNA: anti-double stranded DNA antibody; CI: confidence interval; CRP: C-reactive protein; OR: odds-ratio; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; *statistically significant result (p-value <0.05).

Discussion

Due to advances in SLE treatment and the resulting increase in life expectancy, cardiovascular complications are becoming a major issue in the management of pSLE patients and determinant prognostic factors for the evolution of the disease and the related quality of life (29).

We reviewed 46 cases of pSLE patients (6 to 19 years) with a mean age of 10.53 at SLE diagnosis. The age distribution in our cohort corresponds to the average onset age of 2–16 years and mean age at diagnosis of 3–18 years reported in literature (18, 19). However, the mean age at diagnosis was much lower than that recorded in retrospective reviews from France, Canada, and the United Kingdom where the median age at onset was 12–13 years, with the disease onset occurring after 8 years (30, 31); a study from China recorded the mean age of 12.2 years at diagnosis (32). However, the term of childhood-onset SLE is proposed for all cases with onset prior to 18 years (33).

The majority of our patients were females, with a high female/male ratio of 10.5:1. This ratio is higher than that recorded in several studies including one carried out in a tertiary hospital in Taipei, China which reported a ratio of 82:18 and another study in the United States of America recorded a ratio of 4:3 (6, 32). The ratio in our study appears to be among one of the highest ratios recorded, in reference to previously reported studies (15, 16, 19). On the other hand, female preponderance is more significant in post-pubertal age categories (34).

The prevalence of cardiac complications was found to be 47.8%, which is consistent with the range of data in literature reporting 12% to 54% of cardiac complications (35); especially with data from China, where the prevalence of 47.8% was recorded (32). Valvular heart disease was the most frequent cardiac manifestation diagnosed in 34.8%, followed by pericarditis in 13.0%; while no cardiac involvement was detected in the remaining 52.2% patients. This concurs with the findings of other studies where valvular disease was found in 46% and 66.5% (25, 36). However, some studies found that pericarditis was the most common cardiac manifestation of SLE (80%–90%) which was much higher than the prevalence recorded in our study (23, 37). Other studies reported cardiomegaly to be the most common cardiac manifestation (32). Most parts of the heart can be affected by SLE, including pericardium, myocardium, endocardium, and coronary arteries, with non-specific histological findings in most of the cases (37). Given the inflammatory nature of the disease, serosal tissues including pericardium and pleura are frequently subjected to inflammation (17, 30) which often results in alarming clinical symptoms, such as chest pain, and high CRP levels (38). Regarding pericarditis, previous studies suggested that recurrent episodes are common (37); which highlights the importance of close follow up for those patients after a first diagnosed episode. In addition to these complications, atherosclerosis is becoming concerning issue in children with SLE, increasing the risk of early vascular events (10). In adult, SLE is associated with increased risk of acute myocardial infarction (39); and was shown to be a significant risk factor of coronary atherosclerosis (40).

This study found that the tricuspid valve was involved in the majority of the cases (56.3%); while the mitral valve was involved in 37.5%, pulmonary in 36.3%, and the aortic valve in 18.2% of the cases. This agrees with studies that found the tricuspid valve and mitral valve to be the most commonly affected valves and the aortic valve to be the least affected (25). However, another study found that mitral valve was the most commonly affected valve in 17.1% and tricuspid valve was the least commonly affected in 7.3% cases (6). Aortic was also found to be the most commonly affected valve in one study (36).

We found that cardiac involvement cases were symptomatic in 63.6% and silent in 36.4% of the cases, with 50% of the valvular lesions being silent. This agrees with other studies that have shown that asymptomatic cardiac involvement is common in SLE patients and usually involves the endocardium and pericardium (7, 25, 26, 41). Our study also found that the minimum age of cardiac involvement was 10 years.

However, 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 signs of cardiac involvement of SLE.

Although clinical cardiac abnormalities and findings of structural involvement were not as common in our study as 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 involvements.

In accordance with our findings, cardiac manifestations are rarely reported in the initial presentation of SLE (9.1% cases). This agrees with studies that have shown that the occurrence of cardiac manifestations as the initial presentation of SLE is rare. Common initial manifestation of SLE usually involves renal disease, constitutional symptoms, musculoskeletal, and integumentary system (42). However, 3 cases of cardiac tamponade were reported in literature as the initial presentation of SLE: 2 in young adult patients, a male (43) and a female (44), and another in a 10 year old female patient (42). These cases may be late complications of an undiagnosed SLE pericarditis. On the other hand, an SLE should be ruled out in case of chronic pericarditis or non-infective endocarditis (7).

In this study, a normal chest x-ray was found in 71.7% of all SLE patients including those with cardiac involvement such as pleural effusion associated with pericarditis and cardiomegaly associated with severe valvular heart disease. This was consistent with another study that reported minimal radiographic findings in the setting of serositis involving the pericardium or the pleura (7). Thus, chest x-ray does not exclude cardiac involvement and is not a reliable investigation to screen for cardiac abnormalities, as those changes tend to be non-specific and are likely to be consequences of cardiac manifestations.

The incidence of silent valvular involvement assessed by the echocardiographic examination was also associated with high inflammatory markers, low complement levels but with a normal ECG. The low incidence of ECG abnormalities was also reported in a study where only 13.3% of the cases had an abnormal ECG among 59.9% having abnormalities on echocardiography (25). This would indicate that ECG is not a good screening method, as it only appears abnormal in cases with established cardiac manifestations and does not estimate the possibility of cardiac involvement.

In our study population, the risk of developing cardiovascular complications increases for SLE patients with high inflammatory status, including high CRP levels (p=0.042). However, as data for CRP was not normally distributed in our sample, a logarithmic transformation of original values was performed to complete this analysis. A significant difference was also found in the levels of anti dsDNA (p=0.039); complement C3 (p=0.012) and SLEDAI score (p<0.001) between patients with/without cardiac involvement. These observation are supported further by studies that reported findings of increased CRP in patients with cardiac manifestations (7, 38) and increased anti dsDNA (44).

However, this differs from other studies that found no significant relationship between cardiac manifestations and the levels of complement and anti dsDNA (32, 34). On the other hand, only low complement C3 level and high SLEDAI score were strong predictors of cardiac complications in our study.

Similarly, abnormal echocardiography findings were related to higher levels of inflammatory markers and lower levels of complements, as well as higher SLEDAI score. This was also the case reported in several other studies where the inflammatory marker, CRP was found to be elevated in patients with cardiac manifestations diagnosed on echocardiography (7, 38). However, this differed with a study that showed low levels of complement were not significantly related to the presence of asymptomatic cardiac manifestations (34).

The combination of these data suggests that patients with no apparent cardiac manifestations may be at a higher risk of developing cardiac complications when they tend to have higher levels of anti dsDNA, CRP and SLEDAI Score with lower C3 levels. Thus, patients at high-risk of cardiac involvements are likely to be those in worse condition in all aspects of monitoring the disease activity. All patients with cardiac complication benefited from cardiologic follow-up; however, 50% were lost for follow-up after one year. For the others, 5-year follow-up data showed the following: silent cardiac manifestations remained silent; 4 cases of pericarditis completely recovered and 2 others had intermittent recurrence of pericardial effusion; no case of cardiac tamponade was observed; and none of the valvular lesions required surgical repair or replacement.

Limitations of the study

We had a limited sample size and therefore were limited in analysing risk factors associated with the different types of cardiac manifestations. Criteria for cardiac involvement included only pericarditis, myocarditis and valvular heart disease. Consequently, the prevalence of cardiac involvement may be underestimated, as other cardiac complications such as endocardium thickness and conduction system and coronary arteries abnormalities could not be assessed. Consequently. In addition, because of the retrospective design, we were unable to study all the laboratory markers we intended to, such as antiphospholipids, anti-RO and anti-LA antibodies; which limited the extent of our findings.

Recommendations

We recommend screening for cardiac involvement by echocardiographic examination at least after 3 to 4 years of post diagnosis with SLE or if patients have a high SLEDAI score or high inflammatory markers and low compliments level, as they are considered a reliable method to estimate the disease activity.

We also recommend further studies with a larger sample size for accurate estimation of the incidence of cardiac involvement, its different subtypes and possible establishment of associations with risk factors. In addition, prospective studies are warranted to collect crucial follow-up data, which may provide information on further cardiac involvements or progressive myocardial impairment.

Conclusion

Paediatric-onset SLE is associated with a high incidence of cardiac complications, dominated by valvular heart diseases and pericarditis; and is asymptomatic in half of the cases. As early diagnosis and treatment are crucial to decrease the morbidity and mortality rates related to these complications, a close follow-up of afflicted children by careful clinical examination, laboratory investigations, ECG and echocardiography examination is indicated. Children at high risk of having cardiac complications are likely to be those with high SLE activity, indicated by a high SLEDAI score with varying levels of inflammatory markers and low complement C3 level, regardless of the cardiac symptomatology.

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