Pulmonary involvement in juvenile-onset systemic lupus erythematosus patients asymptomatic for respiratory disease

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Objective The aim of this study was to investigate the presence and frequency of abnormalities in subclinical pulmonary function tests (PFTs) in a group of Egyptian children with juvenile-onset systemic lupus erythematosus (jSLE) asymptomatic for respiratory manifestations.

Patients and methods The study enrolled 20 children with jSLE followed up at the Pediatric Rheumatology Clinic, Cairo University. For all patients, pulmonary function testing was performed including measurement of lung volumes and lung flows using spirometry. Lung diffusion testing was performed using the transfer factor of the lung for carbon monoxide (DLCO) utilizing the single-breath method. Findings were correlated with clinical manifestations and lupus disease activity, and assessed using Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores.

Results NAmong our study group, musculoskeletal, mucocutaneous, hematologic, renal, and neurological manifestations were the most frequent lupus manifestations throughout the course of disease, occurring in 85, 80, 65, 45, and 35% of the patients, respectively. The mean SLEDAI score was 21.3 ± 9.515. Overall, 95% our patients had at least one PFT abnormality within a mean of 4.9 ± 1.94 years after disease onset. Diffusion defect was the most frequent defect detected in 14 (70%) patients, restrictive pathology was found in seven (35%) patients, obstructive pathology was found in six (30%) patients, and mixed restrictive and obstructive pathology in one (5%) patient. In terms of the correlation between PFTs and the SLEDAI, DLCO was correlated positively ($r = 0.37$, $P = 0.05$) to a high SLEDAI, that is, a diffusion defect was significantly evident in patients with high disease activity even without symptoms.

Conclusion Occult pulmonary disease as shown by a PFT occurs frequently in our group of Egyptian patients with childhood-onset systemic lupus erythematosus. *Egypt J Broncho* 2015 9:59–63

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Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic disease involving multiple organs such as the kidneys, skin, and brain [1]. Lung is another organ that can be affected. A number of pulmonary complications including pleurisy, pneumonitis, infectious pneumonia, pulmonary hemorrhage, pulmonary hypertension, and pneumothorax have been reported in patients with SLE [2]. The lung involvement in SLE patients may be a direct involvement, or the lungs may be affected as a consequence of other organ impairments. Pulmonary involvement has also been found in children affected with SLE, with an incidence ranging from 5 to 67%. It is possible that a subclinical disease occurs more frequently than reported previously [3]. The use of more sensitive pulmonary function tests (PFTs) may be a valuable diagnostic tool for the diagnosis of subclinical pulmonary involvement [4]. PFT results in patients with SLE, with and without respiratory symptoms and abnormal chest radiographs, have shown several abnormalities in many studies [5–7]. Restrictive lung disease, measured by PFTs, is the most frequent alteration reported in adult SLE [3]. However, few studies have been carried out on children with juvenile-onset systemic lupus erythematosus (jSLE) to assess this. Also, there is a claim that abnormal PFTs seem to be even more common in children than in adults [8].

The aim of the present work was to explore the frequency and the features of respiratory function tests alterations in a group of Egyptian children with jSLE, with no clinical or radiological manifestations of lung involvement, and explore their clinical significance and correlations.

Patients and methods

Participants

The study randomly enrolled 20 jSLE patients (three male and 17 female, age range 8–23 years, mean 14.8 ± 3.03 years), all fulfilling at least four of the 1997 revised American Rheumatism Association SLE criteria for the diagnosis of SLE [9]. All selected patients were followed up at the Pediatric Rheumatology Clinic, Cairo University Children's Hospital, from January 2011 to December 2011. Disease manifestations

throughout the course of disease were obtained from the patients' follow-up charts. Disease activity was assessed at the time of study enrollment and scored according to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [10]. The disease was considered active when the index was 10 or more. All patients were receiving a low dose of corticosteroids (0.5–1 mg/kg/day) and hydroxychloroquine (200–400 mg/day) from the time of diagnosis of disease, and treated according to the type and extent of organ involvement.

Before undergoing PFTs, all patients underwent a complete clinical evaluation. Information on pulmonary symptoms was obtained by a detailed pretested questionnaire requesting information on dry or productive cough, dyspnea, and cyanosis and chest pain. We included children free from asthma, chronic bronchitis, or emphysema according to the American Education Program criteria. The presence or absence of other organ impairment was also recorded, with a plus or minus, in all patients.

At the time of PFT, hemoglobin levels were measured. A chest radiography was performed for all patients at baseline.

The study was approved by the Cairo University Clinical Research Ethics Committee. Informed consents were obtained from the parents of all participants. All patients' data were kept confidential.

Serological tests

The following laboratory tests were performed for all patients at study enrollment: complement components (C3 and C4); antinuclear antibodies and anti-DNA by indirect immunofluorescence using Hep-2 and *Crithidia luciliae* as substrates, respectively; anticardiolipin, both IgM and IgG by the solid phase radioimmunological technique of Harris and Pierangeli [11], as modified by Lakos *et al.* [12]; and lupus anticoagulant by the Russell's viper venom time.

Pulmonary function tests

Pulmonary function measurements were performed for all patients. Measurement of lung volumes, lung flows, and airway resistance (Raw) was carried out using spirometric techniques. The best of three forced vital capacity (FVC) measurements was registered [13]. Postbronchodilator measurement of the FVC was performed if there were obstructive abnormalities. Seated patients were asked to inhale maximally from tidal respiration to total lung capacity and then rapidly exhale to the fullest extent until no further volume is exhaled at residual volume. The maneuver was performed in a forceful manner to generate a FVC. The volume of air expired during the first second is the FEV_1. Peak expiratory flow rate was measured on the basis of how much the patients could blow out of their lungs in one breath. The tests were performed using the MasterScreen machine (Jaeger, Germany). The percentage–range method was used to determine abnormal values in which a range of 20% above and/or below a patient's predicted mean normal value is considered abnormal [14].

The transfer factor of the lung for carbon monoxide (DLCO) was determined using the single-breath method [15] using the MasterScreen machine (Jeager). The patient was asked to breathe in (inhale) air containing a very small amount of a tracer gas, such as carbon monoxide, hold his/her breath for 10 s, and then rapidly blow it out (exhale). The exhaled gas was tested to determine how much of the tracer gas was absorbed during the breath. Patients were asked not to eat a heavy meal before the test. Diffusion capacity below 80% of the predicted mean value is considered abnormal [14]. Oxygen saturation was measured using a pulse oximeter.

Statistical analysis

The data were coded and entered using the statistical package for the social sciences (SPSS; version 15; SPSS Inc., Chicago, Illinois, USA). Data were summarized using descriptive statistics: mean and SD. The relationship between pulmonary function parameters and disease duration, disease activity, clinical features, and immunological data was assessed by Spearman's correlation.

Results

The study enrolled 20 unrelated Egyptian jSLE children (three male and 17 female; mean age 14.8 ± 3.03 years); the mean disease duration was 4.9 ± 1.94 years (range 2–10 years).

All anthropometric and demographic data are presented in Table 1. The clinical manifestations of our SLE study group are shown in Table 2. Musculoskeletal, mucocutaneous, hematologic, renal, and neurological manifestations were the most frequent manifestations throughout the course of disease, respectively.

None of the patients complained of respiratory symptoms at the time of study enrollment.

Disease activity was assessed using the SLEDAI score at the time of performance of PFTs. The individual values of SLEDAI and the results of the FEV_1, FVC,

Table 1 Anthropometric and demographic data of juvenile-onset systemic lupus erythematosus patients

Number of patients	20
Male/female ratio	3 : 17
Age at study enrollment (years)[a]	14.8 ± 3.037
Weight (kg)[a]	48.8 ± 13.52
Height (cm)[a]	150.8 ± 7.849
Height percentile[a]	18.5 ± 18.51
Age at disease onset (years)[a]	9.9 ± 2.194
Duration of disease (years)[a]	4.9 ± 1.944
Disease activity, SLEDAI[a]	21.3 ± 9.515

SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; [a]Quantitative data are represented as mean ± SD.

Table 2 Clinical and immunological features of the studied 20 patients with juvenile-onset systemic lupus erythematosus throughout the course of disease

Diagnostic criteria	Affected patients [*N* (%)]
Butterfly rash	16 (80)
Discoid lupus	5 (25)
Photosensitivity	17 (85)
Oral or nasopharyngeal ulcers	16 (80)
Arthritis without deformities	17 (85)
Pleurisy or pericarditis	5 (25)
Proteinuria or cellular casts	9 (45)
Neurological manifestations	7 (35)
Hemolytic anemia or leukopenia	13 (65)
Anti-DNA antibodies	12 (60)
ANA antibodies	19 (95)

ANA, antinuclear antibody.

PEF50-PEF25, and DLCO, all expressed as mean score ± SD, are shown in Table 3.

Significant functional impairment, considering alterations in any of the PFTs, was present in 95% of our asymptomatic cases. Restrictive pathology was found in seven (35%) patients, obstructive pathology was found in six (30%) patients, and mixed restrictive and obstructive pathology was found in one (5%) patient. A diffusion defect was detected in 14 (70%) patients.

In terms of the correlation between PFTs and the SLEDAI, DLCO was correlated positively (r = 0.37, P = 0.05) with a high SLEDAI, that is a diffusion defect was significantly evident in patients with high disease activity even without symptoms.

Discussion

Abnormalities of pulmonary function have been found in children with SLE even in the absence of clinical evidence of pulmonary involvement. The present study enrolled 20 Egyptian jSLE patients with no clinical or radiological evidence of chest involvement. Clinical and laboratory data of our study group are in concordance with the manifestations of jSLE commonly found in Egyptian children [16].

Our study showed that highly significant functional lung impairment was present in 95% of jSLE children asymptomatic for chest manifestations. This high incidence of abnormal PFTs in the current study is similar to the results of studies by Delgado *et al.* [17], De Jongste *et al.* [18], and Cerveri *et al.* [19], who reported abnormal PFTs in 62, 87, and 84% of patients with jSLE, respectively. The frequency of PFTs abnormalities in our study group was higher than the frequency in Italian and Canadian studies, which reported abnormal PFTs in 40 and 48% of asymptomatic patients, respectively [3,20].

The restrictive pattern (reduced FVC) represents the main feature of pulmonary involvement in our jSLE patients. This finding may be attributed to parenchymal impairment because of interstitial connective tissue involvement or to reduction of respiratory muscle strength, caused by the disease itself or by the medications, especially the corticosteroids.

The presence of diffusion defects, as measured by DLCO, suggests that the restrictive pattern may be mainly because of parenchymal damage rather than respiratory muscle involvement. As it is not easy to detect respiratory muscle dysfunction (except with specialized electromyography (EMG) for chest muscles) in young patients, because it is difficult to measure maximal in-expiratory mouth pressures correctly, the involvement of respiratory muscles in the restrictive ventilator pattern remains unclear. A report by Decramer *et al.* [21] showed that in adult patients with chronic obstructive pulmonary disease or asthma, respiratory muscle strength and steroid treatment are interrelated despite a relatively low average daily dose of corticosteroids administered in the previous 6 months.

Our study is not without limitations, primarily, the relatively small sample size of jSLE patients, which may be explained by the presence of only one MasterScreen machine for performance of the PFT in the Cairo University Pediatric Hospital, together with the high cost of the tests. We consider this study a preliminary one, and aim to involve a larger number of patients in future studies and to perform PFT as a routine assessment for follow-up of jSLE patients to study the actual prevalence of PFT abnormalities in Egyptian children with jSLE and to intervene as early as possible.

Table 3 Disease activity scores and pulmonary function test results of our study group of juvenile-onset systemic lupus erythematosus patients

Patients	SLEDAI	FEV_1 (%predicted value)	FVC (%predicted value)	PEF25–PEF50 (l/s)	DLCO (ml/min/mmHg)	VA (%) (ml/min/mmHg)
1	22	73	62	81	87.5	80
2	49	104	106	83	109	83
3	20	99	85	151	64	100
4	26	124	129	99	79	70
5	8	91	78	120	70	89
6	10	99.8	84.6	88	87	70
7	8	88	85	100	71	81
8	21	98	85	100	81	92
9	10	128	110	120	79.9	80
10	20	118	118	100	103	76
11	22	82	70	117	63	86
12	18	116	110	115	100	68
13	27	82	79	84	83	60
14	16	92	88.9	76	90	91
15	22	86	74	90	84	67
16	31	118	106	140	100	75
17	15	85	76	72	88	75
18	29	58	50	50	150	120
19	24	96	90	100	77.9	80
20	28	100	97	99	87.5	83
Mean ± SD	21.3 ± 9.5	96.9 ± 17.7	89.175 ± 19.5	99.250 ± 23.5	87.7 ± 191	100 ± 20

DLCO, diffusion lung capacity for carbon monoxide; FEV_1, forced expiratory volume after 1 s; FVC, forced vital capacity; PEF25–50, peak forced expiratory flow at 25–50%; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; VA, alveolar volume.

In conclusion, the present study showed that occult pulmonary disease occurs frequently in childhood-onset SLE, and that PFT abnormalities were found in 95% of these children. Whether progression of these subclinical abnormalities occurs or can be prevented cannot be determined from this study. The results do suggest that serial PFT studies may be useful in assessing the presence of lung involvement in childhood-onset SLE and monitoring the course of the disease.

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Conflicts of interest

There are no conflicts of interest.

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