Pediatric rheumatology

Pulmonary involvement in patients with childhood-onset systemic lupus erythematosus

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Abstract

Objective

Pulmonary involvement is a common finding in adults with systemic lupus erythematosus (SLE). The aim of this study was to investigate the frequency of pulmonary abnormalities in patients with childhood-onset SLE, with particular reference to interstitial lung disease (ILD), and to examine any association between pulmonary abnormalities and other disease-related variables.

Methods

A cohort of 60 Norwegian patients with childhood-onset SLE was examined in a cross-sectional study by high-resolution computed chest tomography (HRCT) and pulmonary function tests (PFT). Median disease duration was 11.2 years. Disease activity, cumulative organ damage and immunological markers were also assessed.

Results

Five patients (8%) had abnormal HRCT findings, including micronodules in four patients and bronchiectasis in one. None of the patients had radiographic evidence of ILD. PFT results were impaired in 37% of the patients, the most frequent pulmonary dysfunction was reduced carbon monoxide diffusing capacity (26%). HRCT findings, disease activity or serology did not correlate with PFTs. Reduced diffusion capacity was associated with smoking (p-value < 0.05).

Conclusion

Lung function was moderately impaired, while the frequency of pulmonary parenchymal involvement was low. There was no radiographic evidence of ILD, which is an unexpected finding given the high frequencies reported in adult SLE patients assessed with HRCT. The results suggests that PFT values are often abnormal, but these are infrequently associated with development of ILD or other substantial parenchymal alterations in childhood-onset SLE, and do not require further HRCT investigation in asymptomatic patients.

Key words

Systemic lupus erythematosus, children, pulmonary function test, interstitial lung diseases.

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Introduction

Pulmonary manifestations in childhood-onset systemic lupus erythematosus (SLE) are the same as those in adults. Pleural disease is the most common, but acute lupus pneumonitis, chronic interstitial lung disease (ILD), pulmonary haemorrhage, diaphragmatic dysfunction and pulmonary hypertension have also been described (1-3). Furthermore, in patients without clinical evidence of respiratory involvement, pulmonary function abnormalities have been reported in a number of studies of childhood-onset and adult SLE (4-7), which suggests the presence of subclinical disease.

The association of interstitial lung disease and SLE has been reported in earlier case-reports (8), but its association became well-recognized first in 1973, when Eisenberg *et al*. reported on 18 cases of SLE complicated by ILD (9). ILD has been found in 54 - 98% in large autopsy studies (10; 11). However, clinically symptomatic ILD is considered to be a less common condition, and the reported frequencies vary between 1 and 14% (2, 9, 12-14).

High-resolution computed tomography (HRCT) is a sensitive and non-invasive technique for detecting pulmonary involvement in SLE (15-17). It has also been shown to be diagnostically superior to plain chest radiography and pulmonary function tests in the evaluation of pleuropulmonary disease in SLE and other connective tissue diseases (17-19). Thus, two studies of HRCT assessment in adult SLE patients have reported an unexpectedly high frequency of ILD, despite the fact that the majority of patients in both studies had no clinical evidence of lung disease (15, 20). Whether HRCT manifestations of ILD are as common in childhood-onset SLE as in the adults reported in those studies, has to our knowledge not been previously investigated.

The aims of this study were firstly to evaluate pulmonary involvement, in particular ILD, in patients with childhood-onset SLE by means of pulmonary function tests (PFT) and HRCT, and secondly to investigate whether respiratory abnormalities were correlated with other disease-related variables.

Patients and methods

This cross-sectional study was performed at the Department of Rheumatology, Rikshospitalet University Hospital (RUH), which serves the majority of the population in southern Norway and has the only paediatric rheumatology department in the country. The study population comprised 60 childhood-onset SLE patients, who had their disease-onset within the age of 16 years and fulfilled the American Rheumatism Association Criteria for classification of systemic lupus erythematosus (21). The study is part of a larger cross-sectional study of 71 childhood-onset SLE patients concerning accumulated organ damage (22), frequency of osteopenia and osteoporosis (23), and alteration in body composition and serum lipids. The majority of the patients in the larger cohort (83%) were recruited from the patient register of RUH and had been registered between January 1980 and June 2003. The other patients were recruited from hospitals in northern and western Norway. One of the 60 patients was a new referral to RUH in september 2003. The patients from RUH were believed to be representative of the vast majority of patients diagnosed with childhood-onset SLE in southern Norway in the time period in question, and the patients from other hospitals were comparable as described in detail elsewhere (22). The 11 patients who participated in the larger cross-sectional study and who chose not to participate in the present study were not significantly different from the other participants with respect to clinical manifestations, disease activity, cumulative organ damage or medication use, but had a significantly lower mean age (19.6 vs. 26.3 years, P value = 0.025) and disease duration (5.1 vs. 11.5 years, p-value = 0.003).

Written consent was obtained from the patients and from parents of patients younger than 16 years. The study was approved by the Regional Ethics Committee for Medical Research.

Data collection and measurements

All patients were examined in accordance with a one-day programme at Rikshospitalet. This included clinical

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examination by the same physician (VL), laboratory tests, pulmonary function tests and radiology. Disease activity and cumulative organ damage were measured by the SLE disease activity index (SLEDAI) (24, 25) and the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) (26, 27), which has been described elsewhere (22). The immnunological markers measured were ANA, anti-ENA, anti-ds-DNA, anti-RNP, anti-SSA and anti-SSB.

Radiology
The patients were submitted to a standard chest radiograph and HRCT (High Resolution Computed Tomography). The CT-examination was performed with a HiSpeed CT/i scanner (GE Medical Systems, Milwaukee, Wis, USA). The images were obtained at 120 kV and 100-200 mA with 1 mm collimation at 10 mm intervals at full inspiration in a supine position. The images were reconstructed with a high-spatial-frequency (bone) algorithm. The lungs were examined from the apex to the base. Six supplementary expiratory scans were obtained in 56 of 60 patients. Readings were performed on printed film or on a PACS (Picture Archiving and Communication System) by one experienced chest radiologists (TMA) with no knowledge of the patients' histories or the PFT results.

CT scans were evaluated for established criteria of ILD (intralobular reticular opacities, interlobular septal thickening, ground glass opacity, architectural distortion and pleural irregularity) and the presence of micronodules, bronchial dilatation and bronchial wall thickening. Presence of abnormal HRCT findings was graded into three categories: 1 = mild, 2 = moderate, 3 = severe. The distribution of disease was assessed in four zones according to the scan levels at the aortic arch, carina, midway between carina and diaphragm, and 1 cm above the right hemidiaphragm.

Air trapping on expiratory images was defined as the presence of lung regions that were more lucent than adjacent lung regions (28). The extent of air trapping was based on a subjective

impression of the reviewer, assessed according to the same, aforementioned scan levels and scored for the whole lung by using a 5-point scale (0=0-1%, 1=1-25%, 2 = 26-50%, 3=51-75%, 4= 76-100% of the cross-sectional area of the lung affected) (29). The potential maximum score for the whole lung could reach 16.

Pulmonary function tests
Spirometry and carbon monoxide (CO) gas transfer were measured using a computerised Sensormedics Vmax 229 pulmonary function unit. Spirometric variables were measured in triplicate and included forced vital capacity (FVC), forced expired volume in one second (FEV_1) and FEV_1/FVC ratio. The highest value of each variable was recorded. The diffusion variables comprised the pulmonary diffusing capacity for CO (DLCO), alveolar volume (VA) and the transfer coefficient (DLCO/VA). All diffusion values reported in the Results and Discussion section are the mean of two trials, corrected for haemoglobin and alveolar volume (DLCO/VA). All tests were measured according to guidelines adopted by the respiratory societies in Northern America (ATS) and Europe (ERS). Reference values were taken from ERS (30, 31).

FVC, FEV_1 and DLCO/VA were regarded as abnormal if the observed value was less than 80% of predicted value. FEV_1/FVC was regarded as abnormal if < 70 % of predicted. Spirometry was performed in all patients, while DLCO was obtained only in 46 patients. FVC and FEV_1 values were not significantly different between patients in whom DLCO was not obtained compared to those who had DLCO measured. Pulmonary dysfunction was defined as either restrictive dysfunction (FVC and DLCO/VA less than 75% pred, and FEV_1/FVC ≥ 70%), obstructive dysfunction (FEV_1/FVC < 70%) or isolated impairment of diffusing capacity (DLCO/VA < 75% pred, FVC > 75% pred and FVC/FEV_1 normal).

Statistical analysis
Differences within patient cohorts were tested by the independent sample *t*-test

for continuous normally distributed variables, the Mann-Whitney test for continuous non-normally distributed variables, and the chi-square test or Fisher's exact test for categorical variables. Correlations were expressed as Pearson correlation coefficients for continuous normally distributed variables and Spearman rank coefficients if either or both variables were non-normally distributed. For all analyses, p-values less than or equal to 0.05 were considered significant. All statistical analyses were performed by the SPSS version 12.0.

Results
Clinical history
Mean age was 28.1 ± 9.5 years and mean disease duration 12.0 ± 8.3 years (median 11.2 years). The demographic variables and disease characteristics are presented in Table I. At the time of evaluation, 11 patients (18%) had dyspnoea on exertion, 5 (8%) had had regular cough, while none reported pleuritic pain. History of prior SLE-related pulmonary involvement included: acute lupus pneumonitis in one patient 19 years prior to the present evaluation, pulmonary embolism in 2 patients secondary to antiphospholipid-syndrome, and pleuritis in 19 patients (32%). None-SLE pulmonary disease was reported in 2 patients in form of asthma that was combined with chronic bronchitis in one patient.

HRCT examination
Five patients (8%) had abnormal HRCT findings, which included micronodules in four patients and bronchiectasis in one patient. The micronodules were located in all lung zones in three patients and in the middle zone in one patient, and scored grade 1 (n = 2) and grade 2 (n = 2). There were no evident signs of ILD in any patients. The presence of micronodules was significantly correlated with disease duration (r = 0.3, p-value = 0.034). No correlations were found between abnormal HRCT findings and disease activity, immunological markers, PFT values, current smoking status or previous smoking status. The mean score for airtrapping was 2.4±2.5. A score of 0 was assigned

Table I. Demographic and disease-related characteristics of children and young adults with childhood-onset systemic lupus erythematosus (SLE).

	Childhood-onset SLE (n = 60)
Female, no. (%)	46 (77)
Age, mean ± SD years (median, range)	28.1 ± 9.5 (27.0, 14.6 – 49.3)
Disease duration, mean ± SD years (median)	12.0 ± 8.3 (11.2)
Age at disease onset, mean ± SD years (median)	12.8 ± 3.0 (13.0)
Caucasian, no. (%)	57 (95)
Smokers ever, no. (%)	20 (33)
Smokers current, no. (%)	14 (23)
SLEDAI, mean ± SD (median)	3.3 ± 4.2 (2.0)
SDI, mean ± SD (median)	1.4 ± 1.7 (1.0)
Nephritis ever *, no. (%)	28 (47)
Hemoglobin < 12.0 g/dl, no. (%)	17 (28)
Anti-ds DNA during disease course, no. (%)	46 (76)
Anti-ds DNA at evaluation, no. (%)	12 (20)
Anti-ENA at evaluation, no. (%)	23 (38)
Anti-RNP at evaluation, no. (%)	10 (17)
Corticosteroid use current, no. (%)	35 (58)
Corticosteroid use ever, no. (%)	57 (95)
Prednisolone, current dose among users, mean ± SD mg (median)	8.9 ± 8.1 (5.0)
Methotrexate use ever, no. (%)	10 (17)
Azathioprine use ever, no. (%)	35 (58)
Cyclophosphamide use ever, no (%)	35 (58)

* Nephritis was defined according to the ARA classification.
SLEDAI: SLE Disease Activity Index; SDI: Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index.

Table II. Pulmonary function test results in pediatric-aged patients and in young adult patients with childhood-onset systemic lupus erythematosus (SLE)*.

	Patients < 20 years (n = 16)	Patients ≥ 20 years (n = 44)
FEV[1]	101.4 ± 11.9 (0%)	89.5 ± 14.1 (21%)
FVC	100.4 ± 9.4 (0%)	96.0 ± 15.0 (14%)
FEV$_1$/FVC	85.4 ± 5.8 (0%)	80.4 ± 6.0 (7%)
DLCO/VA¥	85.0 ± 8.0 (20%)	87.7 ± 14.0 (28%)

* Values are means ± SD. Values in parentheses indicate the percentages of patients with abnormal lung function. FVC, FEV$_1$ and DLCO/VA are given as percentages of predicted values and are considered to be abnormal if they are < 80% of the predicted value. FEV$_1$/FVC is considered to be abnormal if it is < 70% of the predicted value. FVC: forced vital capacity; FEV$_1$: forced expiratory volume in 1s; FEV$_1$/FVC: ratio of expiratory volume in 1s and forced vital capacity; DLCO/VA: diffusion capacity of carbon monoxide corrected for hemoglobin levels and lung volume.
¥DLCO/VA values were obtained only in nine children and 37 young adults.

to 21 patients (38 %) and a score ≥ 1 to 35 patients (62%). Grade of airtrapping did not correlate with PFT results, history of smoking or presence of micronodules. Chest x-rays were normal in all patients in except one, who had diaphragm dysfunction.

Pulmonary function tests
FVC was reduced in six patients (10%) and FEV$_1$ was abnormal in nine (15%) patients. DLCO/VA was impaired in 26% (12 out of 46) of the patients. Overall 37% (17 out of 46) had abnormal PFT results (either abnormal spirometric values and/or abnormal diffusion capacity). DLCO/VA was the most frequently abnormal lung function test, independently of age group (age < 20 years or ≥ 20 years) (Table II, Fig. 1). Isolated impairment of DLCO/VA was found in 9 patients (20%), whereas obstructive and restrictive physiology was seen in three (7%) and one (2%) patients, respectively.
Pulmonary symptoms of dyspnoea on exertion correlated with lower values of FEV$_1$ (r = -0.4, p-value 0.010). FVC and FEV$_1$ were significantly and inversely correlated with cumulative org-

an damage (r = -0.5, p-value < 0.001 for both PFTs), but the results for DLCO/VA reached non-statistical significance (r = -0.2, p-value = 0.175). Abnormal FEV$_1$ values were associated with current smoking (r = 0.3, p-value = 0.023), and a longer disease duration (r = 0.4, p-value = 0.005). Impaired DLCO/VA values did correlate with current smoking, as well as ever smoking (r = -0.3, p-value = 0.028; r = -0.3, p-value = 0.027), whereas a history of former smoking did not (r = -0.1, p-value = 0.7). Smokers had significant lower mean DLCO/VA values (78.8 ± 7.7) than non-smokers (88.6 ± 13.3) (p-value = 0.009). When smokers were removed from the study cohort, the incidence of abnormal DLCO did decline from 27% to 20%, but likewise the incidence of abnormal FEV$_1$ and FVC also declined from 15 -10% and 10-7%, respectively.

Discussion
In the present cohort of 60 childhood-onset SLE patients more than one-third had impairment of pulmonary function as measured by PFTs, while the frequency of HRCT abnormalities was low. Furthermore, none of the patients had radiographical evidence of ILD. The low frequency of HRCT abnormalities (8%) in our patients is in contrast to those of a number of studies of adult SLE patients, which have reported percentages of 38-93% on HRCT abnormalities and 33-60% for the presence of ILD (15, 16, 20). The reason for the discrepancy between their findings and ours is unclear, but the high frequency of ILD reported by Ooi *et al.* can be partly explained by the population selected for that study, since all the patients had been referred because of persistent respiratory symptoms (16). In contrast, Bankier *et al.* (20) selected 48 patients on the basis of abscence of respiratory symptoms, and still found an unexpectedly high frequency of ILD (33%). Furthermore, Fenlon *et al.* found ILD in one-third of their 34 patients (15), the majority of whom also had no respiratory symptoms. The frequency of pulmonary symptoms in our patients was comparable to that noted by Fenlon *et al.* (15).
Another reason for the low frequency

of HRCT abnormalities could be that there was little bias towards severely diseased patients in the selection of patients in the present study. The public health care coverage in Norway and the free access to health care for children are likely to result in diagnosis and hospital admission of most children with lupus disease. Finally, our patients had a lower mean age than those of Bankier *et al.* (20) and Fenlon *et al.* (15) (28.1 versus 39.1 and 41 years, respectively). It would be logical to assume that a younger mean age is associated with a lower frequency of ILD, but whether ILD will evolve in these patients as they get older, or whether ILD is simply less frequent in SLE patients with childhood-onset disease is not known. The presence of micronodules in four of the patients could be a sign of follicular bronchiolitis, which is defined by hyperplasia of bronchus-associated lymphoid tissue, and has been reported to be associated with connective tissue disease among a variety of other conditions (32, 33). However, the findings of micronodules are not specific for SLE and could therefore also be related to other conditions. The lack of pleural HRCT abnormalities might be surprising, since one-third of the patients had a history of pleuritis. Nevertheless, this finding is in line with those of Fenlon *et al.* (15), who also reported on a low incidence of pleural HRCT abnormalities, and suggested that pleural abnormalities are less common than previously suggested, and not more common than in other rheumatic diseases. Evidence of airtrapping was found in 62 % of the patients, but was not associated with abnormal lung function, HRCT pattern or smoking. Similar high frequencies (40-80%) have been reported in several studies in healthy subjects (28, 34, 35), therefore we could not conclude that airtrapping was an abnormal phenomenon in our study group. Diffusing capacity was found to be more severely impaired than FVC and FEV₁. These findings are in line with a number of previously published studies in pediatric-aged and adult SLE patients (5, 7, 36, 37). The reason for the frequent occurrence of abnormal DLCO in SLE patients it not clear. Some of the
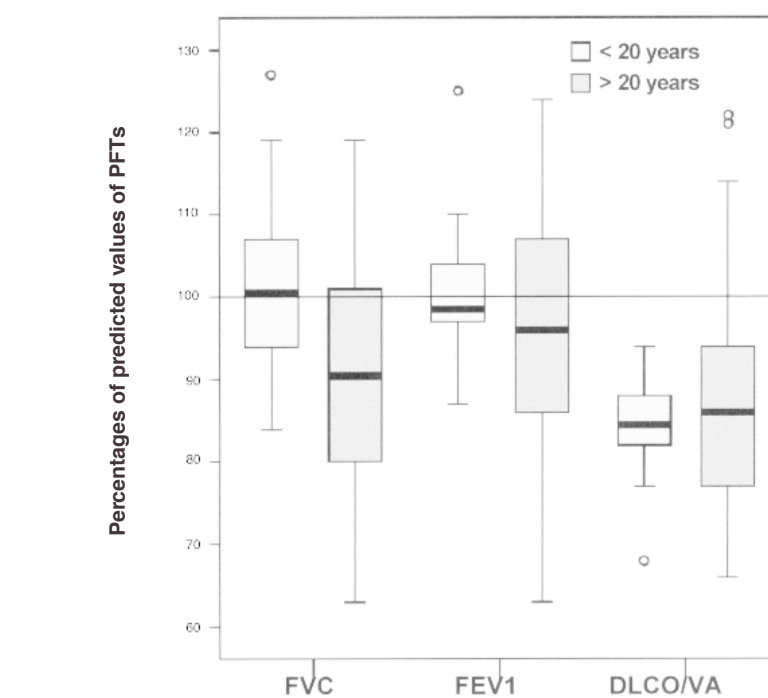

Fig. 1. Boxplot showing pulmonary function test (PFT) results in 60 childhood-onset SLE patients (DLCO was obtained only in 46 patients). The boxes represent the upper and lower quartiles. The line dividing each box is the median value. The circles represent outliers. FVC: forced vital capacity; FEV_1: forced expiratory volume in 1s; DLCO/VA: diffusion capacity of carbon monoxide corrected for hemoglobin levels and lung volume.

underlying mechanisms reported in previous studies include ongoing cell-mediated immune response present in the lungs (38), changes of interstitial lung disease (39) or pulmonary muscle dysfunction (40). Reduced diffusion capacity in our patients was to some degree aggravated by smoking habitus. However, when smokers were removed from the study, DLCO still remained to be the most frequently impaired PFT. This finding is in line with a controlled study of non-smoking SLE patients, which also showed DLCO to be the most commonly impaired PFT (36). However, the abnormalities in PFT results, which may indicate subclinical lung disease, were not accompanied by HRCT abnormalities.

The relatively limited sample size in the present study may be a drawback. Another limitation is the lack of longitudinal data on PFT values. However, the population studied is believed to be representative of childhood-onset SLE patients with respect to clinical manifestations, cumulative organ damage (22) and the male/female ratio in children with SLE (41). Another strength

of the study may be, that there was no selection bias in favour of more severe cases. Furthermore, the study also evaluates pulmonary involvement in childhood-onset SLE patients, who have entered adulthood, on which there is little information in the literature. Although previously high doses of radiation been reported for HRCT examination (42), HRCT as it is currently performed in clinical practice, is considered to be a low-dose examination, and produces only a radiation dose of 5-10% that of conventional contiguous CT (43, 44).

To conclude, in the present study one-third of the childhood-onset SLE patients had impairment of PFT results, most commonly in form of reduced DLCO/VA, while the frequency of HRCT abnormalities was modest. Furthermore, there was no evidence of ILD, which was an unexpected finding given the high frequencies reported in adult SLE patients assessed with HRCT. The results suggests that PFT values are often abnormal, but these are infrequently associated with development of ILD or other substantial paren-

chymal alterations in childhood-onset SLE, and do not require further HRCT investigation in asymptomatic patients.

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