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Prevalence of Respiratory Function Abnormalities in Asymptomatic Chinese Patients with Juvenile Onset Systemic Lupus Erythematosus

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Abstract

Objectives: To determine the prevalence and features of respiratory function alterations in asymptomatic Chinese patients with juvenile onset systemic erythematosus (JSLE) and to assess its relationship with clinical and immunological parameters. ***Methods:*** Twenty-two Chinese patients with JSLE followed up at our Rheumatology Clinic were recruited. Each underwent pulmonary function test (PFT) and completed a respiratory questionnaire. Four were excluded because of past history of pulmonary disease. Abnormal respiratory function findings if present would be correlated with the disease duration, disease activity, organ involvement, clinical features and immunological findings using multiple regression analysis. ***Results:*** All 18 patients analysed were totally free of pulmonary symptoms and disease. Thirteen patients (72%) had abnormal PFT results. Ten patients (56%) had decreased diffusion capacity of the lung (DLCO). Among them, 2 had restrictive lung pattern and one had mixed pattern while 7 had isolated DLCO impairment. Disease duration and renal involvement were both found to be significantly associated with decreased DLCO (p=0.037 and p=0.035 respectively). However, both factors became insignificant after multiple regression analysis. Neurological lupus was significantly associated with decreased FEF 25-75% and FEF 75% (p value 0.03 and p<0.001 respectively). ***Conclusion:*** Asymptomatic Chinese patients with JSLE and no prior pulmonary involvement showed frequent PFT abnormalities with decreased DLCO being the most common impairment. Neurological involvement was the only factor found to be significantly associated with abnormal lung function parameters. We speculate that decreased DLCO could be related to high occurrence of SLE-associated pulmonary hypertension in Chinese. Further in-depth evaluation and long term follow up study is warranted.

Key words Children; Chinese; Respiratory function; Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder affecting multiple organ systems including the skin, musculoskeletal system, kidneys, central nervous system, blood and respiratory system. Pulmonary involvement is frequent in adults with SLE and the disease spectrum ranges from asymptomatic pleuritis to life threatening pulmonary haemorrhage. The lungs may be directly affected or impaired as a result of other organ involvement.[1] The overall reported prevalence of pulmonary involvement in adult SLE patients varies from 10% to 100% depending on the stage of disease and the criteria used to define such involvement. The reported incidence of clinically significant respiratory disease ranged from 3% to 17% at disease onset and 3-36% over the course of the disease.[2] Many of the patients with abnormal pulmonary functions were asymptomatic. Pulmonary function test has been recommended for early detection of lung involvement

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in patients with SLE before onset of symptoms.[3]

Pulmonary involvement has also been reported in children with juvenile onset systemic lupus erythematosus (JSLE). There have been a few studies on pulmonary function tests in children with JSLE only and none included Chinese population. It is well known that there is ethnic difference in clinical manifestations of SLE. We therefore attempted to perform a study in Chinese children having JSLE but asymptomatic for pulmonary diseases to document the prevalence of pulmonary function abnormalities, to determine the clinical and immunological correlation of abnormal pulmonary function tests if present.

Methods

Subjects

All patients with a diagnosis of JSLE attending follow-up at the Queen Mary Hospital, a tertiary referral center were screened. Only patients who fulfilled the American Rheumatism Association (ARA) criteria for diagnosis of SLE, who were over the age of 6 years and proficient in performing pulmonary function test PFT were recruited. Each underwent pulmonary function test and completed a respiratory questionnaire.

Pulmonary Function Tests PFTs

PFTs were performed between December 2002 and March 2003 in random order. All PFTs were performed according to the recommended standard American Thoracic Society protocol, using a Sensor Medics VMAX22 spirometer (Sensor Medics, Yorba Linda, USA) by the same nurse.[4] Pulmonary function results were expressed as percentages of predicted normal values.[5] This included percentage of predicted forced expiratory volume in the 1st second (FEV_1), forced vital capacity (FVC), residual volume (RV), total lung capacity (TLC), forced expiratory flow rates in the middle half of the FVC (FEF 25-75%), forced expiratory flow rate at 50% and 75% of the FVC (FEF 50% and FEF 75% respectively). Diffusion capacity of carbon monoxide was measured by single breath technique and corrected for haemoglobin concentration ($DLCO_{adj}$). Abnormal pulmonary function tests were categorised into restrictive pattern (FEV_1/FVC >80%, TLC <80%), obstructive pattern (FEV_1 <80%, FEV_1/FVC <80%), mixed restrictive and obstructive pattern, and small airway disease (FEF 25-75% or FEF 75% <50%). Impaired $DLCO_{adj}$ was defined as $DLCO_{adj}$ <80% predicted values.

Clinical and Immunological Parameters

Patients' records were reviewed for disease duration, disease activity, involvement of various organs, presence of Raynand's phenomenon and immunological parameters: anti-nuclear antibodies (ANA), anti-double stranded DNA (anti-ds DNA), lupus anticoagulant (LAC), IgG and IgM anti-cardiolipin (aCL), antineutrophil cytoplasmic antibodies (ANCA) including PR3 and MPO, anti-extractable nuclear antigen (anti-ENA) including anti-Smith (Sm), anti-Ro, anti-La, anti Sc1-70, anti RNP and other unidentifiable anti-ENA component. The disease duration was recorded as the number of years, rounded to the nearest year. The disease activity was based upon the SLE Disease Activity Index (SLEDAI) and Systemic Lupus International Collaborating Clinics (SLICC) scoring system given at the follow-up nearest the date within one month of the PFT. The immunological parameters were defined as follows:

1. Presence or absence ANA;
2. Any presence of anti-dsDNA was considered to be positive; the highest level of anti-dsDNA recorded was used to differentiate between patients with the high levels (>450 IU/ml) and low levels (<450 IU/ml);
3. IgG and IgM aCL antibodies were considered to be positive only if there was a three-fold increase compared with the normal range;
4. LAC was tested by the haematology laboratory and recorded as present or not;
5. Anti-ENA and its components were recorded as positive or negative.

Statistical Tests

Unpaired t-tests and Chi-squared tests were used to correlate the lung function test results with the disease duration, disease activity, organ involvement, clinical features and immunological parameters. Multiple regression tests were performed when more than one of the above was significantly correlated with one particular lung function parameter.

Results

Twenty-seven patients were eligible. One patient was not in Hong Kong, one was not psychologically fit because of active neuro-psychiatric lupus and three were unable to attend during the designated time period. Four patients were excluded for past history of pulmonary disease. A total of

18 patients were included.

Patient demographics and clinical features are summarised in Table 1. All patients were of Chinese ethnicity. All except one were female. The mean age was 16 years (range 8-24 years) and mean disease duration was 6.2 years (range 1-13 years). The mean disease activity level of the patients was low using both the SLEDAI and SLICC scoring system. The data for activity level was not available for one patient. All patients were non-smokers and did not have any respiratory symptoms. More than half of the patients had non-erosive arthritis and cutaneous manifestations. Half of the patients had renal involvement and oral ulcers. All other features occurred in less than half of the patients. ANA and anti-ds DNA were found in all patients. The other immunological tests were performed when indicated in some of the patients only. The immunological parameters are summarised in Table 2.

The PFT results are summarised in Table 3. The result of the RV was invalid in one patient. Thirteen patients (72%) had abnormal PFT results. Among them, 7 patients (39%) had isolated $DLCO_{adj}$ impairment, 2 (12%) had restrictive pattern with decreased $DLCO_{adj}$, 2 (12%) had restrictive pattern and 1 showed a mixed pattern with decreased $DLCO_{adj}$ (6%). One patient had an obstructive pattern (6%) but she did not have any symptoms of chronic cough or asthma. No patients fulfilled the criteria for small airway disease.

Univariate analysis showed that both the disease duration and renal involvement were significantly associated with decreased $DLCO_{adj}$ (p=0.037 and p=0.035 respectively).

Table 1 Demographic data and clinical features

Patient Demographics	
Total number of patients	18
Male: Female ratio	1:17
Mean age in years (range)	16 (8-24)
Mean disease duration in years (range)	6.2 (1-13)
Mean disease activity (range)	
SLEDAI	2.35 (0-8)
SLICC	0.11 (0-1)
Respiratory symptoms and history	
History of asthma and symptoms	0
Presence of dyspnoea	0
Presence of chest pain	0
Personal history of smoking	0
Family history: Smoking	5
Asthma	3
Lupus clinical features	
Malar rash	13
Discoid rash	1
Photosensitivity	6
Oral ulcers	9
Pericardial effusion	3
Arthritis	15
Renal disorder	9
Neurological disorder	6
Raynaud's phenomenon	2

Table 2 Immunological parameters

Test	Number with positive test/ Number with test done
ANA	18/18
Anti-ds DNA	18/18
High	8
Low	10
Coomb's	1/14
Lupus anticoagulant	0/13
Anticardiolipin antibody	
IgG	2/17
IgM	1/17
ANCA	8/14
MPO	0/8
PR3	1/8
Anti-ENA	12/17
Anti Ro	9/12
Anti Sc170	1/12
Anti Sm	1/12
Anti Jo	0/12
Anti RNP	3/12
Anti La	2/12
Others	4/12

Table 3 Pulmonary function test (PFT) indices

PFT indices	*n*	Mean (SD)	Range
FEV_1 (%predicted)	18	96.7 (19.8)	53-140
FVC (% predicted)	18	97.8 (18.5)	71-133
FEV_1/FVC	18	89.2 (7.5)	67-97
FEF 25-75 (%predicted)	18	93.4 (24.6)	23-134
FEF 50 (%predicted)	18	90.8 (23.3)	62-130
FEF 75 (%predicted)	18	93.1 (34.0)	70-148
TLC (%predicted)	18	88.3 (14.2)	68-112
RV (%predicted)	17	77.9 (31.3)	38-129
RV/TLC (%)	17	87.4 (29.1)	42-138
$DLCO_{adj}$ (%)	18	76.8 (14.1)	51-117

However, both factors became insignificant after multiple regression analysis. Neurological lupus was also significantly associated with decreased FEF 25-75% and FEF 75% (p value 0.03 and p<0.001 respectively). None of the clinical or immunological parameters were found to be significantly associated with any of the abnormal PFT patterns.

Discussion

Our study showed a significant overall functional lung impairment in 72% of the JSLE patients with no known pulmonary disease or involvement. There are only a few studies on pulmonary function in children with JSLE.[6-12] Four of the studies included both symptomatic and asymptomatic patients.[7-9,12] In the study by Al-Abbad et al, 9 out of 26 asymptomatic patients had abnormal PFTs but the exact types of abnormalities were not clearly stated. Three studies included asymptomatic patients.[6,10,11] The results of Singsen's study was only available in a textbook where full details were not described. Cerveri et al reported baseline FVC and DLCO results only and direct comparison cannot be made with their cohort. Compared to Trapani et al's study, the overall abnormal PFTs in our study is much higher (72% versus 40%). The apparent higher rate of abnormal PFTs could be attributed to the older age of our cohort compared with those in Trapani et al's study (mean age 16 years versus 13.5 years). Lung function abnormalities in adults are frequent, occurring in as many as 88% of patients without clinical or radiological abnormalities.[2,13,14] The longer disease duration in our cohort (6.2 years versus 66 months) might also explain the discrepancy between the pulmonary function abnormalities in the two studies. However there was no significant correlation between pulmonary parameters and disease duration found at baseline in Tranpani et al's study. Our study showed that disease duration was correlated with $DLCO_{adj}$ but this became insignificant after multiple logistic regression for adjustment of other potential risks factors. Studies with greater sample sizes are needed to confirm the association between disease duration and abnormal pulmonary function tests. Ethnicity might also account for the difference in prevalence of abnormal pulmonary function. It has been reported that central nervous system (CNS) and pulmonary involvement as well as anti-Sm and anti-RNP antibodies are less prevalent in Greek SLE patients than that reported in the literature.[15] In comparison to Caucasian patients with SLE, Chinese patients are less likely to have serositis or haematologic disorders at diagnosis but more likely to develop proteinuria, CNS or other major organ involvement over the course of the disease.[16] The presence of renal involvement correlated with impaired $DLCO_{adj}$ indirectly suggests that pulmonary involvement may also be more frequent in Chinese than Caucasian.

Our study concurred with many studies which reported that impaired $DLCO_{adj}$, occurring alone or with other abnormal pulmonary lung functions, was the most commonly reported PFT abnormality in adult and juvenile onset SLE patients.[3,8,14,17,18] Impaired $DLCO_{adj}$ in patients with restrictive pattern suggests parenchymal lung disease due to connective tissue involvement. This was present in 2 of our patients. Chest radiographs of these patients were normal. Further imaging studies will be carried out to document the presence of parenchymal lung disease. However, when impaired $DLCO_{adj}$ occurs alone, one should be alert for the early development of pulmonary hypertension which can be primary or secondary related to multiple factors including pulmonary thrombo-embolism and valvular heart disease.[19] The prevalence of pulmonary hypertension varies in different studies from 5% to 14% [20] and is usually of milder severity compared to patients with systemic sclerosis.[21] Shen et al reported that pulmonary hypertension was common in Chinese patients with SLE (11%).[22] Nakano et al found that $DLCO_{adj}$ impairments were correlated with Raynaud's phenomenon.[3] Studies showed that 75% of patients with SLE-associated pulmonary hypertension have Raynaud's phenomenon, compared with only 25% to 40% of other patients with SLE.[20,23] We therefore speculate that the apparent high prevalence of isolated impaired $DLCO_{adj}$ could be due to the higher occurrence of pulmonary hypertension in our cohort. Among the 7 patients with isolated impaired $DLCO_{adj}$, chest radiographs were available in 4 and were all normal. Doppler echocardiographic studies (a less accurate but less invasive investigation than cardiac catheterisation for documenting presence of pulmonary hypertension) will be performed later.

Two of our patients had restrictive lung pattern without impairment of $DLCO_{adj}$. Respiratory muscle impairment has to be considered especially for patients who have been put on long-term corticosteroids. Patients with SLE-associated respiratory muscle weakness typically do not have signs or symptoms of significant generalised muscle weakness.[24] More detailed investigation will be required for these 2 patients.

One patient had obstructive lung pattern and 1 with mixed restrictive and obstructive pattern in our study. Both patterns are rarely reported in patients with SLE or JSLE. Follow up for respiratory symptoms is warranted and a trial of bronchodilator therapy may be considered should symptoms occur.

Another interesting observation in our study is the association of neurological lupus and decreased FEF 25-75% and FEF 75% (p value 0.03 and p<0.001 respectively). Decreased FEF 25-75% and FEF 75% suggests small airway disease. Trapani et al also found that cerebral lupus was associated with abnormal PFTs.[11] However, it was associated with decreased FVC, which suggests either parenchymal disease or respiratory muscle weakness. No plausible explanation was offered in their study. This discrepancy between our findings with Trapani et al's study requires further study for clarification.

Many studies have also tried to correlate PFT abnormalities in SLE patients with their immunological parameters but most were inconclusive. Trapani et al reported that JSLE patients with anti ENA positive results had significantly more decreased FVC than those without.[11] Decreased FVC could be due to respiratory muscle weakness or parenchymal lung disease. The author suggested that the presence of anti-ENA represented a subgroup of lupus that resembled systemic scleroderma or mixed connective tissue disease where restrictive lung pattern is commonly reported. We could not find any relationship between abnormal PFTs and any of the immunological parameters.

The clinical significance of abnormal PFTs is that it has a direct impact on the long-term follow up and management of JSLE patients. Several longitudinal studies showed no evidence of progressive lung abnormality in asymptomatic patients with PFT impairment, however the follow up intervals were only within 6 months.[3,11] Cervari et al showed a high prevalence of functional abnormalities of the lungs in children with clinically active connective tissue diseases, including JSLE but not those in remission.[25] Three years later, they re-evaluated the sub-group of children with JSLE and found that a decrease in SLE activity was associated with an improvement in pulmonary function. The presence of early isolated functional abnormalities was not associated with development of lung disease at the second evaluation.[10] Nevertheless, long term studies are warranted as most patients with JSLE will have disease activity persisting into adulthood.

In summary, sub-clinical pulmonary impairment is a common finding in Chinese children with JSLE that have no prior clinical evidence of lung involvement. Isolated decreased $DLCO_{adj}$ was the commonest type of abnormality identified. More in-depth evaluation including radiological studies and Doppler echocardiography is warranted to delineate the possible underlying cause for the impairment in $DLCO_{adj}$. Long-term studies are also recommended for early detection of potential reversible pulmonary problems in patients with JSLE.

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