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Extent of Subclinical Pulmonary Involvement in Childhood Onset Systemic Lupus Erythematosus in the Sultanate of Oman

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Abstract

Objectives: The aim of this study was to investigate the frequency of pulmonary function abnormalities in clinically asymptomatic children with Systemic Lupus Erythematosus and to determine the relationship of these abnormalities to clinical, laboratory, and immunological parameters as well as to disease activity.

Methods: Forty-two children with childhood onset Systemic Lupus Erythematosus were included in this study. Demographic, clinical, laboratory and immunological parameters, as well as disease activity were assessed. Pulmonary function tests (PFT) were performed routinely to screen for subclinical lung disease.

Results: Out of the 42 children, 19% (n=8) had clinical evidence of pulmonary involvement. The patients with no clinical evidence of pulmonary involvement (n=34) represent the study cohort. From our cohort of patients with no clinical evidence of pulmonary involvement 79% (n=27) had PFT abnormality; including 62% (n=21) had reduced FVC, 71% (n=24) had reduced FEV1, and 67% (n=12) had reduced DLCO. Similarly, 56% (n=15) had a restrictive PFT pattern, and 2.6% (n=2) had an obstructive PFT pattern, while 33% (n=7) had an isolated impairment of diffusion capacity. Due to small sample size; it was not possible to find a statistically significant difference between the cohort of asymptomatic SLE patients with abnormal PFT findings (n=27) and those with normal PFT findings (n=7) in terms of clinical, laboratory, immunological or disease activity index score.

Conclusion: Subclinical lung disease, as demonstrated by abnormal PFT in patients with normal radiographs, may be common but should be interpreted with caution as an early sign of lung disease. Although PFT studies do not correlate well with pulmonary symptoms in patients with childhood onset SLE, they nevertheless provide objective quantification of the type and severity of the functional lesions.

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Keywords: Systemic lupus erythematosus; Pulmonary; Prevalence; Oman.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that may affect many organs. Pulmonary involvement is a common finding in children affected with SLE, with an incidence ranging from 5-67%.[1] The spectrum of disease varies between different ethnic groups with Afro-Caribbean reportedly having more pulmonary features than Caucasians.[2] The most frequently described pleuropulmonary manifestations of childhood onset SLE include pleural effusions, pleuritis, as well as acute and chronic pneumonitis. Others include diffuse interstitial lung disease, muscle and/or diaphragm dysfunction, pneumothorax, pulmonary hypertension and alveolar hemorrhage. However, subclinical lung disease occurs in as many as 60 to 70 percent of patients who are tested by a sensitive diagnostic tool such as pulmonary function test.[3,4]

The aim of this study was to investigate the frequency of pulmonary function abnormalities in clinically asymptomatic children with SLE in Oman and to determine the relationship of these abnormalities to clinical, laboratory and immunological parameters as well as to disease activity.

Methods

The hospital records of children with childhood onset SLE who are followed up at the pediatric rheumatology clinic at Sultan Qaboos University Hospital (SQUH), in Sultanate of Oman, were retrospectively reviewed over a ten year period (2001 - 2011). All the patients included in the study were Omani children diagnosed with SLE before 14 years of age. The diagnosis of SLE was based on the 1982 revised criteria for the classification of SLE.[5] All children fulfilled at least four of the American College of Rheumatology (ACR) criteria and had been diagnosed with SLE at least six months prior to inclusion in the study.

A data collection format was designed which included the following parameters: age, gender, age at diagnosis, and disease duration, as well as clinical and immunological data. The clinical manifestations studied were the major clinical manifestations of SLE including mucocutanous, articular, cardio-

respiratory, gastrointestinal, hematological, and central nervous system involvement. The immunological parameters recorded included antinuclear antibodies (ANA), which is determined by immunofluorescence using Hep-2 cells as the substrate. Anti-double stranded DNA (anti-dsDNA) was measured qualitatively using enzyme linked immunosorbent assay technique. Extractable nuclear antigens including anti-RNP, Sm, SS-A, SS-B, and anticardiolipin were assessed by a standardized ELISA technique.

Disease activity was assessed and scored according to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). The original SLEDAI is a weighted, cumulative index of lupus disease activity, and the SELENA SLEDAI represents further refinement. The total score falls between 0 and 105, with higher scores representing increased disease activity. The SLEDAI has been shown to be a valid and reliable disease activity measure in multiple patient groups, and has also been shown to be sensitive to changes in disease activity in children. Disease activity measurement was recorded at the time of pulmonary function tests (PFT).

Pulmonary function tests were performed routinely at baseline and at yearly intervals to screen for subclinical lung disease for all patients with childhood onset SLE. Because pulmonary function testing is technically challenging and time consuming in young children, the test was performed in children above 6 years of age only. The parameters of PFTs that were recorded included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and diffusion capacity of carbon monoxide (DLCO).

Spirometry and carbon monoxide (CO) gas transfer were measured using Medgraphics Elite Series Plethysmograph. The actual results of PFT except for DLCO are expressed as the percentage of predicted values. DLCO was determined with the single breath method and the values were corrected for hemoglobin concentration. Maximal expiratory flows were obtained with the subjects breathing room air; the best of the three measurements was used to calculate the forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). All tests were measured according to guidelines adopted by the American Thoracic Society and Europe Respiratory Society (ERS). Reference values were taken from ERS.[6,7]

Any pulmonary function value >85% of predicted values was considered as normal; while values <75% were considered severely abnormal; and values 75-84% were considered mild/moderate abnormality. Pulmonary dysfunction was defined as either restrictive dysfunction (FVC and DLCO less than 75% predicted and FEV1/FVC >70%), obstructive dysfunction (FEV1/FVC <70%) or isolated impairment of diffusion capacity (DLCO <75%, FVC > 75% predicted and FVC/FEV1 normal).

Descriptive statistics were used to describe the data. For categorical variables, frequencies and percentages were reported. Differences between groups (normal and abnormal FEV status) were analyzed using Pearson's χ^2 tests (or Fisher's exact tests for cells less than 5). For continuous variables, means and standard deviations were presented and analyses were conducted using Student's *t-test*. An a *priori* two-tailed level of significance was traditionally set at the 0.05 level. Statistical analyses were conducted using STATA version 11.1 (STATA Corporation, College Station, TX).

Results

Out of the 42 childhood onset SLE patients followed-up at Sultan Qaboos University Hospital Pediatric Rheumatology Clinic; 19% (n=8) had pulmonary involvement of which three had pulmonary hemorrhage, three had pleural effusion, and two had pneumonitis. The rest of the patients with no clinical evidence of pulmonary involvement (n=34) represent the cohort for current study. Spirometry was performed in all patients, while DLCO was obtained in 18 patients only.

Table 1 illustrates the demographic data of cohort of patients with childhood onset SLE with no clinical evidence of pulmonary involvement. The average age at diagnosis was 8.2 (±2.7) years, mean disease duration was 6.1 (± 3.8) years and the current mean age was 14.2 (±4.2) years; representing largely young girls (82%). The clinical and laboratory features of our cohort of patients are summarized in Table 2. The most prominent clinical characteristics of childhood onset SLE were fever (n=23; 68%), nephritis and proteinuria (n=22; 65%); mucocutaneous manifestations (n=21; 62%), arthritis (n=21; 62%), and weight loss (n=15; 44%). With regards to serological parameters of the study cohort (Table 3); almost all the children were ANA (n=32; 94%) and anti-dsDNA (n=29; 85%) positive. Table 4 outlines other biochemical parameters of the study cohort. Almost all SLE children had low C3 (88%) and C4 (85%), while 79% had high ESR.

Table 1: Demographic characteristics of patients with Childhood Onset SLE.

Characteristic	All (N=34)
Female gender, n (%)	28 (82%)
Age, mean (±SD), years	14.2 (±4.2)
Age at diagnosis,, mean (±SD), years	8.2 (±2.7)
Disease duration, mean (±SD), years	6.1 (±3.8)

SLE=Systemic lupus erythematosus

Table 2: Clinical characteristics of patients with Childhood Onset SLE.

Characteristic	All (N=34)
Fever	23 (68%)
Weight loss	15 (44%)
Mucocutaneous	21 (62%)
Arthritis	21 (62%)
Nephritis	22 (65%)
Edema	10 (29%)
Hematuria	16 (47%)
Proteinuria	22 (65%)
Cardiac	4 (12%)
Abdominal pain	13 (38%)
Lymphadenopathy	12 (35%)
Hepatomegaly	7 (21%)
Splenomegaly	2 (6%)

Table 3: Serological characteristics of patients with Childhood onset SLE.

Characteristic	All (N=34)
Positive ANA	32 (94%)
Anti-dsDNA	29 (85%)
Ro/SSA	5 (15%)
La/SSB	6 (18%)
Anti-RNP	4 (12%)
Anti-Sm	7 (21%)

SLE=Systemic lupus erythematosus

Table 4: Other biochemical parameters of patients with Childhood onset SLE stratified by abnormal FEV status (N=34).

Characteristic	All (N=34)
Low C3	30 (88%)
Low C4	29 (85%)
High CRP	14 (41%)
High ESR	27 (79%)

SLE=Systemic lupus erythematosus

Table 5 demonstrates the extent of pulmonary involvement in clinically asymptomatic patients with childhood onset SLE. Up to 79% (n=27) of the children had an abnormality in pulmonary function test despite being asymptomatic. Sixty-two percent (n=21) had reduced FVC, 71% (n=24) had reduced FEV1, while 67% (n=12) had reduced DLCO. Out of the cohort of patients with abnormal PFT (n=27); 56% (n=15) had a restrictive PFT pattern, 2.6% (n=2) had an obstructive PFT pattern, and 33% (n=7) had an isolated impairment of diffusion capacity. Due to the small sample size, we were not able to find statistically significant difference between the cohort of clinically asymptomatic patients with abnormal PFT finding (n=27) and those with normal PFT findings (n=7) in terms of clinical, laboratory, immunological or disease activity index score (SLEDAI).

Table 5: PFT results in patients with Childhood onset SLE.

Status, n (%)	FVC (N=34)	FEV1 (N=34)	DLCO (N=18)
Normal	12 (35%)	10 (29%)	6 (33%)
Mild/moderate abnormality	9 (26%)	10 (29%)	3 (17%)
Severe abnormality	13 (38%)	14 (41%)	9 (50%)

SLE=Systemic lupus erythematosus; FEV=Forced expiratory volume; FVC= Forced vital capacity, DLCO= diffusion capacity of carbon monoxide; Percent is column percentage.

Discussion

Our cohort of patients represents one of the two Pediatric Rheumatology Centers in the Sultanate of Oman. The population studied is believed to be representative of childhood onset SLE with respect to clinical manifestation, cumulative organ damage and sex ratio in Oman. While acknowledging the limited size of this study cohort, our study illustrates the spectrum of pulmonary manifestations of childhood onset SLE. The study shows that 83% (n=35) of children followed up at our center with SLE (n=42) had pulmonary involvement. Furthermore, 19% (n=8) of patients had clinical evidence of pulmonary involvement, while 64% (n=27) had evidence subclinical disease manifested by an abnormal PFT.

Pulmonary disease is a common manifestation of SLE in children. The pulmonary manifestations and frequency of occurrence in childhood onset SLE appears to be similar to that described in adult onset.[2] Pleuritis is the most common pulmonary manifestation of SLE, occurring in 30-35% of children with pulmonary involvement.[8] Acute pneumonitis, which can be confused with pneumonia, is an uncommon manifestation occurring in 10-15% of the patients.[9] However, chronic interstitial lung disease is seen with increasing frequency in children with SLE who live into their twenties and thirties. Shrinking lung syndrome, which is due to muscle and/or diaphragm dysfunction and may progress to severe respiratory dysfunction, has been reported in children.[3,10] Alveolar hemorrhage is a rare but serious form of pulmonary involvement in patients with SLE with significant mortality and morbidity occurring in less than 5% of patients with childhood onset SLE.[9,11] It is interesting to note that pulmonary hemorrhage as an initial manifestation of childhood onset SLE is occurring more frequently (37.5%) in our cohort of patients than reported in the literature, whilst the frequency of pleuritis (37.5%) and pneumonitis (25%) are similar. Despite a high mortality rate, our patients with pulmonary hemorrhage were all treated successfully with corticosteroids and immunosuppressive agents.

PFT in SLE patients has been used for many years as a diagnostic tool for early detection of subclinical pulmonary involvement. It is a sensitive and practical tool which is used in many centers. Our study shows that in our cohort of patients who were clinically asymptomatic and with no radiological evidence of pulmonary disease (n=34), 79% (n=27) had functional lung impairment. Fifty-six percent had restrictive PFT pattern while 2.6% had obstructive PFT pattern. A diffusion defect was observed in about one third of the patients. Our results show slightly increased values to what has been reported in both adult and childhood onset SLE studies.[12,13] Andonopulous et al. in a controlled study, evaluated the pulmonary function of 70 SLE patients, abnormalities were found in 63% of lupus patients with isolated decrease in DLCO in 31% of patients.[12] Nakano et al. described that similar findings were seen in a retrospective analysis of 110 patients with active SLE. Reduced DLCO was frequently observed even in asymptomatic patients (39%). Restrictive impairment was seen in 8% of the patients.[13] Similar pulmonary abnormalities were described in few limited studies in children with SLE.[14-16] Al-Abbd et al. performed PFTs on 33 children with SLE (n=26 asymptomatic and n=7 symptomatic). Overall, 48% of the cohort had abnormal PFT specifically, 35% of asymptomatic children had abnormal pulmonary functions.[17] In another smaller study of 13 children with SLE, functional lung impairment was present in 40% of subjects at baseline; in 60% patients at 6 months;

and in 33% of patients at 12 months. In this study, there was no correlation between altered PFTs and disease duration, activity and/or immunological findings.

Subclinical lung disease, as demonstrated by abnormal pulmonary function testing in patients with normal radiographs, may be common but should be interpreted with caution as an early sign of progressive lung disease. Other factors such as disease duration, disease activity and/or immunological factors may correlate with such defects. In our cohort of patients, we found no such co-relation due to small sample size. In the literature, there are controversies with regards to the significance of these PFT abnormalities in clinically asymptomatic patients. In a cohort of 60 patients with childhood onset SLE, Lilleby et al. found PFT impairment in 37% of the patients, with 26% having reduced carbon monoxide diffusion capacity impairment. However, high resolution chest tomography (HRCT), disease activity or serology did not correlate with PFT abnormality.[18] They concluded that abnormal PFT in asymptomatic patients with childhood onset SLE do not need further radiological imaging. In contrast, many adult studies report unusually high prevalence of HRCT abnormalities, suggestive of interstitial lung disease in asymptomatic SLE patients with normal PFTs.[19-22]

Conclusion

In summary, although pulmonary function studies do not correlate well with pulmonary symptoms in patients with childhood onset SLE, they nevertheless provide objective quantification of the type and severity of the functional lesions. Serial tests may be helpful in monitoring disease activity in childhood SLE.

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References

1. Trapani S, Camiciottoli G, Ermini M, Castellani W, Falcini F. Pulmonary involvement in juvenile systemic lupus erythematosus: a study on lung function in patients asymptomatic for respiratory disease. Lupus 1998;7(8):545-550.
2. Tucker LB, Menon S, Schaller JG, Isenberg DA. Adult- and childhood-onset systemic lupus erythematosus: a comparison of onset, clinical features, serology, and outcome. Br J Rheumatol 1995 Sep;34(9):866-872.
3. Delgado EA, Malleson PN, Pirie GE, Petty RE. The pulmonary manifestations of childhood onset systemic lupus erythematosus. Semin Arthritis Rheum 1990 Apr;19(5):285-293.
4. Mochizuki T, Aotsuka S, Satoh T. Clinical and laboratory features of lupus patients with complicating pulmonary disease. Respir Med 1999 Feb;93(2):95-101.
5. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982 Nov;25(11):1271-1277.
6. Cotes JE, Chinn DJ, Quanjer PH, Roca J, Yernault JC; Official Statement of the European Respiratory Society. Standardization of the measurement of transfer factor (diffusing capacity). Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Eur Respir J Suppl 1993 Mar;16:41-52.
7. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC; Official Statement of the European Respiratory Society. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Eur Respir J Suppl 1993 Mar;16:5-40.
8. Caeiro F, Michielson FM, Bernstein R, Hughes GR, Ansell BM. Systemic lupus erythematosus in childhood. Ann Rheum Dis 1981 Aug;40(4):325-331.
9. Beresford MW, Cleary AG, Sills JA, Couriel J, Davidson JE. Cardio-pulmonary involvement in juvenile systemic lupus erythematosus. Lupus 2005;14(2):152-158.
10. Thompson PJ, Dhillon DP, Ledingham J, Turner-Warwick M. Shrinking lungs, diaphragmatic dysfunction, and systemic lupus erythematosus. Am Rev Respir Dis 1985 Oct;132(4):926-928.
11. Miller RW, Salcedo JR, Fink RJ, Murphy TM, Magilavy DB. Pulmonary hemorrhage in pediatric patients with systemic lupus erythematosus. J Pediatr 1986 Apr;108(4):576-579.
12. Andonopoulos AP, Constantopoulos SH, Galanopoulou V, Drosos AA, Acritidis NC, Moutsopoulos HM. Pulmonary function of nonsmoking patients with systemic lupus erythematosus. Chest 1988 Aug;94(2):312-315.
13. Nakano M, Hasegawa H, Takada T, Ito S, Muramatsu Y, Satoh M, et al. Pulmonary diffusion capacity in patients with systemic lupus erythematosus. Respirology 2002 Mar;7(1):45-49.
14. Singsen BH, Platzker CG. (1990) Pulmonary involvement in the rheumatic disorders of children. In:Kending El, Chernick V (eds) disorders of the respiratory tract in children, 5th edn. WB saudners, Philadelphia, pp 890-916.
15. Cerveri I, Bruschi C, Ravelli A, Zoia MC, Fanfulla F, Zonta L, et al. Pulmonary function in childhood connective tissue diseases. Eur Respir J 1992 Jun;5(6):733-738.
16. Cerveri I, Fanfulla F, Ravelli A, Zoia MC, Ramenghi B, Spagnolatti L, et al. Pulmonary function in children with systemic lupus erythematosus. Thorax 1996 Apr;51(4):424-428.
17. Al-Abbad AJ, Cabral DA, Sanatani S, Sandor GG, Seear M, Petty RE, et al. Echocardiography and pulmonary function testing in childhood onset systemic lupus erythematosus. Lupus 2001;10(1):32-37.
18. Lilleby V, Aaløkken TM, Johansen B, Førre O. Pulmonary involvement in patients with childhood-onset systemic lupus erythematosus. Clin Exp Rheumatol 2006 Mar-Apr;24(2):203-208.
19. Sant SM, Doran M, Fenelon HM, Breatnach ES. Pleuropulmonary abnormalities in patients with systemic lupus erythematosus: assessment with high resolution computed tomography, chest radiography and pulmonary function tests. Clin Exp Rheumatol 1997 Sep-Oct;15(5):507-513.
20. Afeltra A, Zennaro D, Garzia P, Gigante A, Vadacca M, Ruggiero A, et al. Prevalence of interstitial lung involvement in patients with connective tissue diseases assessed with high-resolution computed tomography. Scand J Rheumatol 2006 Sep-Oct;35(5):388-394.
21. Ooi GC, Ngan H, Peh WC, Mok MY, Ip M. Systemic lupus erythematosus patients with respiratory symptoms: the value of HRCT. Clin Radiol 1997 Oct;52(10):775-781.
22. Fenlon HM, Doran M, Sant SM, Breatnach E. High-resolution chest CT in systemic lupus erythematosus. AJR Am J Roentgenol 1996 Feb;166(2):301-307.