Respiratory tract disease in systemic lupus erythematosus

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SUMMARY Respiratory tract involvement is common in adults with systemic lupus erythematosus (SLE). Although SLE in children usually follows a more severe course than in adults, there are few reports on pulmonary disease and lung function in children with SLE. We performed lung function tests and chest x ray examinations in eight children with SLE (mean age 11.1 years), three of whom presented with pulmonary symptoms. A high prevalence of lung involvement was found, including interstitial or localised infiltrations, pleural effusion, a restrictive impairment of lung function, and dysfunction of the diaphragm. Three patients required artificial ventilation. Two main mechanisms of ventilatory impairment seem to occur in children with SLE: firstly, acute interstitial pneumonia, which rapidly improves on treatment with steroids, and, secondly, restriction of lung volume, mainly due to respiratory muscle weakness.

Systemic lupus erythematosus (SLE) is characterised by the production of auto-antibodies that damage multiple organ systems. Respiratory tract abnormalities are frequently observed in adult patients with SLE. The most common findings are sterile pleural effusion and pneumonia, which is usually due to infection.^{1–7} Interstitial lung disease is found in only 3% of adult patients with SLE.¹ Lung function studies in adults, however, have revealed a high incidence of abnormalities even in the absence of clinically apparent lung disease.² Volume restriction, decreased compliance, reduced diffusion capacity, and hyperventilation with arterial hypoxia at rest or during exercise have been reported.^{2–6} In adult patients with SLE the degree of lung function impairment correlated poorly with clinical and x ray findings.⁴ Lung function seemed to be the most sensitive indicator of pulmonary involvement.⁴ SLE is uncommon in children aged 15 years or younger. When SLE does occur in this age group it often seems to follow a more severe course than in adults.^{7–8} Pleural and pulmonary involvement have been reported in up to 70% of paediatric patients with SLE, pleural effusion being the most common finding.^{9–11} There are few data on lung function in children with SLE: Singen and Platzker found restrictive defects in seven (35%) and diffusion impairment in five (25%) of 20 patients with SLE

(mean age 15.5 years) without clinical or radiological evidence of pulmonary disease.¹¹

We have diagnosed SLE in eight children aged 6–14 years in the Sophia Children's Hospital since 1980. In some of these patients pulmonary involvement was a prominent feature early in the course of the disease. We therefore examined all the cases for the presence and extent of respiratory tract involvement. Four patients were followed for two to three years.

Methods

SLE was diagnosed according to the criteria published by the American Rheumatism Association.¹² These criteria were fulfilled by four girls and four boys aged 6–14 years, who were referred to the Sophia Children's Hospital between 1980 and 1985 because of multisystem disease. Treatment with steroids (prednisolone 60 mg/m² per day in three divided doses) was begun in all patients when the diagnosis of SLE had been confirmed.

Evaluation of respiratory tract involvement included physical examination, chest x ray examinations (anteroposterior inspiration and expiration and right transverse views), and lung function studies. Lung function was measured for the first time as soon as permitted by the clinical condition of

the patients and, in two cases who came to our attention later, two and three years after diagnosis. Lung volumes were determined with a water locked spirometer (Mijnhardt), and total lung capacity was measured with the helium dilution method. Flow-volume curves were obtained using a Fleisch heated pneumotachograph. To determine if airway obstruction was present together with volume reduction, the maximal expiratory flows were normalised for total lung capacity,¹³ and the shape of the flow-volume loops was examined qualitatively. In all patients lung function was measured before and after bronchodilatation (fenoterol 0.4 mg administered by metered dose inhaler). Expiratory semi-static compliance measurements were performed according to the technique described by Zapletal

*et al.*¹⁴ The diffusion capacity for carbon monoxide (D_{CO}) was measured with a single breath technique,¹⁵ except in case 2 where accurate measurement was not possible because of a severe restriction of her vital capacity. The transdiaphragmatic pressure gradient was measured as the difference in oesophageal and gastric pressures during a maximal inspiratory effort against a closed valve at 0% and 30% of vital capacity, as described by Vanmeenen *et al.*¹⁶

We used the reference values of Zapletal *et al* for lung volumes and compliance,^{14 17} of Michaelson *et al* for flows corrected for total lung capacity,¹³ and of Vanmeenen *et al* for transdiaphragmatic pressures.¹⁶ Our own measurements in healthy school children aged 10 to 20 years were used as a

Table 1 Clinical and laboratory data* of the eight children with systemic lupus erythematosus

	Case No							
	1	2	3	4	5	6	7	8
Age (years)	6	9	10	12	12	13	13	14
Sex	F	F	F	M	M	M	M	F
Weight loss	+	+	+	-	+	+	-	+
Fever	+	+	+	-	+	-	-	+
Arthritis/arthritis/myalgia	+	+	+	+	+	+	+	+
Heart:								
Cardiomegaly	+	+	-	+	+	-	-	+
Pericardial effusion	+	+	-	+	-	-	-	+
Conduction defect	+	+	+	+	+	-	-	-
Cardiac failure	+	-	-	+	-	-	-	-
Hypertension	+	+	-	+	+	-	-	-
Lungs:								
Pleurisy	+	+	-	+	+	+	-	+
Pulmonary infiltrates	+	+	+	-	-	-	-	+
Respiratory insufficiency	+	-	-	+	-	-	-	+
Skin and mucous membranes:								
Butterfly rash	-	+	-	-	+	+	-	-
Exanthema	+	+	+	-	+	+	-	-
Purpura	+	-	-	+	-	-	-	+
Subcutaneous fat necrosis	-	+	-	-	-	-	-	-
Mucous membrane lesions	+	-	-	-	+	-	-	-
Nervous system:								
Convulsions	-	+	-	+	-	-	-	-
Central nervous system damage (paresis etc)	+	-	+	-	-	-	-	-
Psychosis	-	-	-	+	-	-	-	-
Kidneys:								
Nephritis	+	+	+	+	+	+	+	+
Renal insufficiency	+	-	-	+	-	+	-	-
Gastrointestinal:								
Enteritis	+	-	-	-	-	-	-	-
Haemorrhage	+	-	+	-	-	-	-	-
Lymphadenopathy, splenomegaly, hepatomegaly	+	-	+	-	-	-	-	-
Blood:								
Anaemia (Coombs test positive)	+	+	+	+	+	-	-	-
Lymphocytopenia	-	+	+	+	+	-	-	-
Thrombocytopenia	+	+	+	+	-	+	-	+
Raised erythrocyte sedimentation rate	+	+	+	-	+	+	+	+

* At any time during the course of the disease.

reference for D_{CO} values (H Stam. Unpublished observations).

Results

The presenting symptoms were pulmonary shadows (cases 2, 6, and 8), with respiratory insufficiency (case 8), nephritis (case 4), arthritis (case 3), and general malaise, fever, and arthralgia (cases 1, 5, and 7).

Clinical and laboratory data are summarised in Table 1. All patients eventually developed nephritis,

and three (cases 1, 4, and 6) progressed to renal insufficiency requiring haemodialysis.

Chest x ray examinations revealed abnormalities in seven patients (Table 2), varying from isolated pleural effusion to interstitial shadowing, pleural effusion, elevation and insufficient excursion of the diaphragm, and narrow intercostal spaces with downward slanting of the ribs (atonic chest) (Fig. 1). Sputum cultures were always negative, except in case 1, where *Staphylococcus aureus* and *Candida albicans* were isolated later in the course of the disease. We measured lung function in all the patients except case 1. Artificial ventilation was necessary until this patient died. Ventilator settings indicated that compliance and diffusion capacity were highly abnormal.

The results of lung function measurements are shown in Table 3. Spirometric data showed a severe restriction in four patients, mainly due to a reduced inspiratory reserve volume. The forced expiratory volume in one second:forced vital capacity ratio, expiratory flows corrected for total lung capacity, and the patterns of the flow-volume curves were normal. No changes were observed after administration of fenoterol.

Table 2 Results of initial chest x ray examinations in eight children with systemic lupus erythematosus

	Case No							
	1	2	3	4	5	6	7	8
Pleural effusion	+	+	-	+	+	+	-	+
Pulmonary shadowing:								
Diffuse interstitial	+	+	-	-	-	-	-	+
Patchy	+	+	+	-	-	-	-	-
Atelectasis	+	+	-	+	-	-	-	-
Diaphragm elevation	+	+	+	-	+	-	-	-
Atonic chest configuration	+	+	+	-	+	-	-	-

Fig. 1 Chest x ray of case 1 made shortly after admission, showing diffuse interstitial shadowing of both lower lung fields, pleural effusion on the left side, enlargement of the heart and hilar structures, broadening of the superior mediastinum, atonic configuration of the chest (narrow intercostal spaces, downward slanting of the ribs in inspiration), and elevation of the diaphragm.

Table 3 Results of lung function tests in seven children with systemic lupus erythematosus, measured at first presentation

		Case No						
		7	8	6	4	3*	5	2†
TLC	(% predicted)	102	89	82	68	65	60	37
IRV	(% TLC)	37	46	42	57	38	34	18
TV	(% TLC)	7	9	14	11	16	20	25
ERV	(% TLC)	31	18	18	13	24	21	13
RV	(% TLC)	25	27	26	19	22	25	44
FVC	(% predicted)	101	85	74	75	70	59	33
FEV ₁	(% FVC)	90	90	85	80	84	96	84
MEF _{50-75%} FVC	(% predicted)	135	86	73	64	92	89	34
MEF _{50%} FVC/TLC	(% predicted)	124	96	118	82	141	143	80
MEF _{25%} FVC	(% predicted)	110	79	53	58	68	91	23
MEF _{25%} FVC/TLC	(% predicted)	94	82	57	68	155	127	59
C _{1,sl} %TLC/cm H ₂ O	(% predicted)	94	87	77	115	—	76	63
D _{CO} /BSA	(% predicted)	87	65	55	80	58	69	—
D _{CO} /TLC	(% predicted)	96	81	107	97	113	125	—

*Measured three years after diagnosis.

†Measured two years after diagnosis.

Abbreviations: TLC=total lung capacity; IRV=inspiratory reserve volume; TV=tidal volume; ERV=expiratory reserve volume; RV=residual volume; FVC=forced vital capacity; FEV₁=forced expiratory volume in one second; MEF_{50-75%}FVC=maximal expiratory flow after 50-75% of the FVC is expired; C_{1,sl}=semistatic compliance; D_{CO}=carbon monoxide diffusion capacity; BSA=body surface area.

Semistatic compliance measurements were abnormal in three patients (below 80% predicted). In all six subjects in whom it was measured D_{CO} was diminished for body surface area but normal or increased for the remaining lung volume. In two subjects with a restriction in lung capacity (cases 2 and 5) and one with normal lung function at that time (case 8) we measured transdiaphragmatic pressures at 0% and 30% of vital capacity (Fig. 2). During a maximal inspiratory effort against a closed valve, decreased transdiaphragmatic pressure gradi-

Fig. 2 Results of transdiaphragmatic pressure measurements in cases 2, 5, and 8. The gradient between transpleural and intra-abdominal pressures during maximal inspiratory efforts against a closed valve at 0% and 30% of vital capacity are shown. Reference values, shown by broken lines, are from the paper by Vanmeenen et al.¹⁶

ents were found in cases 2 and 5 and normal values in case 8. Conventional electromyographic studies were performed in cases 2 and 4 and indicated the presence of myopathy.

In four patients we had the opportunity to repeat lung function measurements at roughly half yearly intervals (Fig. 3). Most subjects had one or more relapses of SLE after tapering the treatment with steroids. Six patients were eventually given azathioprine (2-4 mg/kg/day) because of steroid toxicity or frequent relapses with progression to renal insufficiency. Three patients showed a gradual improvement in vital capacity over several years, which was unaffected by changes in the activity of

Fig. 3 Follow up data of vital capacity measurements in four children with systemic lupus erythematosus (cases 2, 5, 6, and 8).

SLE. A stable restriction was present in case 2, which was not influenced by SLE relapses. In case 8 we measured lung function before SLE was diagnosed. She was initially referred because of fatigue and had no other symptoms suggestive of SLE. At that time no abnormalities in lung function were detected. A few months later she developed the acute severe interstitial pneumonia that led to the diagnosis of SLE. She required artificial ventilation for two weeks and improved dramatically after the beginning of treatment with steroids. One week after the artificial ventilation was stopped the lung function measurements were repeated and indicated a mild restriction, which improved slowly in the following years (Fig. 3).

Blood gases, determined in arterialised capillary blood samples, were normal in all the patients except during acute episodes of respiratory insufficiency in cases 1, 4, and 8. Case 1 developed a progressive interstitial pneumonia and needed artificial ventilation with high airway pressures and oxygen for one month. She then died due to massive gastrointestinal blood loss. Autopsy showed a widespread necrotising vasculitis affecting all organ systems. The lungs showed interstitial inflammation and a diffuse haemorrhagic tracheobronchitis. Case 4, who was on haemodialysis, required ventilatory support several times because of acute pulmonary oedema. This was probably due to fluid overload. This patient died three years after diagnosis from pulmonary oedema, seizures, and cardiac arrhythmia.

Discussion

Our findings suggest a high prevalence of lung disease in childhood SLE. The most common findings were pleural effusion and volume restriction; three of our patients presented with severe respiratory symptoms.

Interstitial lung disease, which is infrequently seen in adults with SLE,¹ was present on x ray examination in three and was histologically confirmed in one of our eight patients. Treatment with steroids seemed to be clinically effective in two of these subjects (cases 2 and 8). The normal diffusion capacity when corrected for lung volume in case 8 suggested that no important interstitial disease had remained. A considerable restriction of vital capacity persisted, however, in case 2 and was also found in three patients without radiological signs of interstitial disease and normal diffusion capacity (cases 4, 5, and 6). Martens *et al* found normal or only slightly lowered $D_{CO}/\text{total lung capacity}$ values in seven adult patients with SLE with a restriction in lung volume.¹⁸ These findings suggest that this

restriction is not only due to interstitial lung disease but that other abnormalities may be present as well.

Dysfunction of the diaphragm and other respiratory muscles in adult patients with SLE, which may be due to myopathy, has been reported recently.¹⁸⁻²⁰ We found markedly decreased transdiaphragmatic pressures in two patients who had restriction in lung volumes (cases 2 and 5). One of these patients (case 2) had clinical and electromyographic signs of myopathy in other muscles. This suggests that the respiratory muscle strength was impaired due to myopathy. The decreased compliance in three patients, two of whom had no radiological signs of interstitial lung disease, might have been caused mainly by muscle weakness with diminished inflation of normal lung tissue and not by interstitial fibrosis and inflammation. This possibility has been suggested by Martens *et al*, who found normalisation of the compliance after passive lung inflation to normal volume in adult patients with SLE.¹⁸ For technical reasons, this could not be performed in our patients. Multiple small atelectases, which have been described in lungs from adult patients with SLE, might also have contributed to an increased lung stiffness and a restriction in lung volume. Maximal expiratory flows were low in four patients. Normal values were obtained, however, after correction for total lung capacity. Together with the normal shape of the flow-volume loops, this makes airway obstruction unlikely.

Localised pulmonary shadows were present in three patients. Although we cannot exclude that this may have been due to infection, this seems unlikely because initially no micro-organisms were cultured from the sputum, which was usually scanty and clear. Furthermore, treatment with antibiotics was always ineffective, and these pulmonary shadows resolved during treatment with steroids. Secondary infection was only documented in case 1, who deteriorated despite maximal therapeutic efforts.

The severity of lung disease was not related to the overall activity of the disease. Several patients experienced relapses and, for instance, developed rapidly progressive glomerulonephritis without a decrease in lung function. Furthermore, in three of the four patients we followed the lung function improved gradually regardless of SLE relapses. This contrasts with the course of the renal disease in SLE, which tends to progress to renal failure despite treatment.

In conclusion, we have found a high prevalence of disease of the respiratory tract in childhood SLE. Our findings suggest that there are two main reasons for the impairment in lung function in these children. The first is interstitial pneumonia, which follows an acute course and improves on treatment

with steroids. The second is respiratory muscle weakness, which is not particularly disabling and can persist for years.

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