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Pulmonary Manifestations of Rheumatologic Diseases in Pediatric

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Abstract

Objectives: To describe the pulmonary manifestations in rheumatic diseases in pediatrics - systemic lupus erythematosus (SLE), juvenile dermatomyositis (JDM), systemic scleroderma (SSc), linear scleroderma (LS), and mixed connective tissue disease (MCTD)-and to correlate these findings with clinical manifestations, imaging and pulmonary function tests.

Methods: A retrospective cross-sectional analysis was performed. We evaluated patients with rheumatic disorders followed at the Rheumatology Department of Hospital Pequeno Príncipe from January 2000 to July 2012. All patients diagnosed with SSc, as well as patients with SLE, JDM, MCTD and LS who had pulmonary symptoms or worsening of their underlying disease, were submitted to chest radiography (CXR), chest high resolution computed tomography (HRCT) and pulmonary function tests (PFTs).

Results: A sample of 193 patients was obtained for this study. Thirty-eight percent of them were submitted to CXR and chest HRCT, with or without PFTs. Within all patients included in this study, 37% had some degree of pulmonary involvement, verified in at least one test. The groups who presented higher rates of pulmonary involvement were the SSc (100%) and the MCTD (46%). Patients with SLE and JDM had similar results, presenting pulmonary involvement in 35% of cases, and LS had the lowest rate of respiratory system involvement, with 25% of patients affected. In one quarter of the cases, the abnormalities found were due to infections. In the remaining three quarters pulmonary involvement was due to the underlying disease, and a large spectrum of manifestations was detected.

Conclusions: Pulmonary involvement often occurs in systemic rheumatic diseases. There is a variety of manifestations in all rheumatic disorders, and there are no pathognomonic signs of pulmonary involvement in each disease. Health professionals should be aware of the possibility of pulmonary involvement in rheumatic disorders, in order to detect it early and initiate adequate treatment precociously, to improve the long term prognosis.

Keywords: Connective tissue diseases; Lupus Erythematosus; systemic; Scleroderma; Diffuse; Scleroderma, Localized; Amyopathic dermatomyositis; Mixed Connective tissue disease; Lung Diseases

Introduction

Rheumatic diseases are a heterogeneous group of immune mediated inflammatory diseases, which present a wide spectrum of systemic manifestations [1-9]. Lungs are among the most affected organs in these disorders [1-9]. There are several forms of pulmonary involvement in rheumatic disorders, not only by the disease itself, but also by infections and toxicity of medications used for treatment [1-4]. Thus, there are no specific patterns of pulmonary involvement in each of these diseases [1,5,7]. The clinical presentation, the prognosis and response to therapy depend on the histological pattern, as well as the type of disease [5,7].

In pediatric patients, some of the rheumatologic diseases that can present with pulmonary manifestations are: Systemic Lupus Erythematosus (SLE), Systemic Scleroderma (SSc), Linear Scleroderma (LS), Juvenile Dermatomyositis (JDM) and Mixed Connective Tissue Disease (MCTD).

In patients with SLE, about 50% have some form of pulmonary involvement during the course of the disease [10-15]. Pleuritis, besides being the most common pulmonary manifestation of SLE, is one of eleven ACR criteria for the disease classification. Other possible manifestations are pleural effusion, pneumonitis, interstitial fibrosis, pulmonary hypertension, pulmonary hemorrhage, pulmonary embolism and shrinking lung syndrome [1,3,10-14].

Scleroderma is divided into systemic and localized forms. In SSc, the lung is the second most affected organ, surpassed only by the esophagus. About 70% to 90% of patients with SSc have pulmonary involvement, which is the leading cause of death in adult age [1,3,16-20]. The disease can manifest as restrictive lung disease, pulmonary hypertension, pleurisy and aspiration pneumonia [3,16-20]. In LS the involvement of other organs, other than the skin, is very rare, though it is described as a possible complication of the disease3.

Up to 50% of adults with dermatomyositis (DM) have pulmonary involvement represented by fibrosis and pneumonitis [1,3,21-23]. Aspiration pneumonia and chest muscle weakness can also be observed [21-23]. These abnormalities are rarely found in children [3]

Since MCTD is defined as an overlap of other rheumatologic diseases, pulmonary manifestations vary widely. The most common manifestation is interstitial pulmonary fibrosis, while pulmonary hypertension is the most frequent cause of death [3,24,25].

Pulmonary involvement is extremely common in rheumatologic disorders, not only in adults but also in children and adolescents [2-4]. Hence, it is important that health professionals be aware of the possibility of pulmonary involvement in pediatric rheumatologic diseases, and how to investigate them, in order to start treatment early and to improve the long term prognosis [1-9,14,17,24].

Despite the importance of the subject, there are few scientific studies on this topic in the pediatric population, and the available data in the literature regarding the pulmonary involvement in this age group are scarce.

The aim of this study was to describe the main pulmonary manifestations related to rheumatic diseases in pediatrics-SLE, JDM, SSc, LS and MCTD-and to correlate these findings to clinical manifestations, imaging and pulmonary function tests.

Methods

A retrospective cross-sectional analysis of patients with SLE, SSc, LS, JDM and MCTD was performed to evaluate the prevalence of pulmonary involvement in each of these diseases, and the most common types of involvement. All patients who attended the Pediatric Rheumatology outpatient clinic of Hospital Pequeno Príncipe from January 2000 to July 2012, and who had a confirmed diagnosis of these disorders, were included in the study. Patients were included in the study if they were less than 18 years old at the first outpatient visit.

All patients diagnosed with SSc were submitted to chest radiography (CXR), chest high-resolution computed tomography (HRCT) and pulmonary function tests (PFTs), regardless of symptoms, due to the high prevalence of pulmonary involvement in this disorder. The same tests were ordered for patients with SLE, JDM, MCTD, and LS who presented symptoms suggestive of pulmonary involvement-prolonged cough (over 15 days), dyspnea and pleuritic chest pain-or had aggravation of the underlying disease, evidenced by history and physical examination, associated with increased serum levels of inflammatory markers.

All tests were performed at Hospital Pequeno Príncipe, and were evaluated by radiologists (CXR and chest HRCT) and pulmonologists (PFTs) of the Hospital staff.

Patients who did not fulfill diagnostic criteria for the described diseases were excluded from the study, as well as those with pulmonary co morbidities, and patients who had their first outpatient appointment after being 18 years old.

The collected data were grouped and a descriptive analysis was performed. Results were presented in graphs and tables, made in the Microsoft Excel® and Word® programs version 14. Qualitative variables were analyzed by Fisher's exact test, and quantitative variables, by the Student T- test. A confidence interval of 95% (CI=95%) was used. The software XL–Stat was used for statistical analysis.

Variables analyzed were gender, age at diagnosis, presence of respiratory symptoms (prolonged cough, dyspnea and pleuritic chest pain), CXR, chest HRCT and PFTs.

This research was performed in accordance with the Declaration of Helsinki guidelines, and was approved by the Ethics Committee of Hospital Pequeno Príncipe.

Results

After reviewing the medical records and applying the inclusion and exclusion criteria mentioned above, we obtained a total sample of 193 patients. One hundred and twenty eight of these were diagnosed with SLE, 37 with JDM, 7 with SSc, 8 with LS, and 13 with MCTD. The demographic and clinical characteristics of all patients are listed in Table 1.

	SLE n = 128	**JDM n = 37**	**SSc n = 7**	**LS n = 8**	**MCTD n = 13**	**TOTAL n = 193**
Female N (%)	102 (80)	26 (70)	3 (43)	7 (88)	12 (92)	150 (78)
Average age at diagnosis (mean ± SD)	11y9m (±3)	8y6m (±3)	8y11m (±3)	8y4m (±4)	9y8m (±2)	10y9m (±3)
Time to diagnosis						
<1 month N (%)	33 (26)	3 (8)	2 (29)	0	0	38 (20)
1 to 12 months N (%)	62 (49)	28 (76)	1 (14)	2 (25)	10 (77)	103 (53)
1 to 3 years N (%)	16 (12)	4 (11)	4 (57)	6 (75)	3 (23)	33 (17)
>3 years N (%)	17 (13)	2 (5)	0	0	0	19 (10)
Respiratory Symptoms* N (%)	23 (18)	4 (11)	4 (57)	0	3 (23)	34 (18)
Prolonged cough N (%)	9 (7)	3 (8)	3 (43)	0	1 (8)	16 (8)
Dyspnea N (%)	15 (11)	2 (5)	3 (43)	0	2 (16)	22 (11)
Pleuritic Chest pain N (%)	7 (5)	0	0	0	1 (8)	8 (4)
Pulmonary investigation performed N (%)	36 (29)	16 (42)	7 (100)	6 (75)	8 (61)	73 (38)

Immediate N (%)	27 (21)	8 (21)	3 (43)	4 (50)	2 (15)	44 (23)
<12 months N (%)	4 (3)	0	1 (14)	0	2 (15)	7 (3)
>12 months N (%)	6 (5)	8 (21)	3 (43)	2 (25)	4 (31)	23 (12)
Presence of pulmonary involvement N (%)	45 (35)	13 (35)	7 (100)	2 (25)	6 (46)	72 (37)

Table 1: Description of the demographic and clinical characteristics of patients. *Eleven patients presented more than 1 respiratory symptom.

	SLE N = 83	JDM N= 26	SSc N= 7	LS N=6	MCTD N=12	TOTAL N=134
Unilateral PE N (%)	12 (14)	1 (4)	0	0	2(16)	15(11)
Bilateral PE N (%)	6 (17)	0	0	0	0	6 (4)
Pulmonary edema N (%)	2 (2)	1 (4)	0	0	0	3 (2)
Pulmonary hemorrhage N (%)	1 (1)	0	0	0	0	1 (1)
Opacity N (%)	9 (11)	2 (8)	1 (14)	1 (17)	2(16)	15(11)
Congestive pattern N (%)	3 (4)	0	0	0	1 (8)	4 (3)
Pneumothorax N (%)	1 (1)	0	0	0	0	1 (1)
Pleural thickening N (%)	1 (1)	0	0	0	1 (8)	3 (2)
Bronchial involvement N (%)	1 (1)	2 (8)	0	0	0	3 (2)
Infection N (%)	12(14)	5 (19)	0	1 (17)	1 (8)	19 (14)

Table 2 :Abnormal results in chest radiographies. PE=Pleural Effusion. Note: Ten patients had more than one alteration in chest X-ray.

The female gender prevailed in almost all rheumatic diseases, except in SSc, in which males had a slight predominance. Scleroderma (systemic and linear) was the disorder which presented greater delay in diagnosis (most cases were diagnosed between 1 and 3 years after the onset of symptoms). The other diseases were diagnosed usually during the first year of onset. The average age of diagnosis was 10 years and 9 months.

Thirty-four patients had respiratory symptoms, and eleven had more than one symptom. Dyspnea was the most common symptom found, followed by prolonged cough and pleuritic chest pain.

Thirty-eight percent of patients (38) were submitted to pulmonary investigation with CXR and chest HRCT, with or without PFTs. All tests were performed in all patients with SSc, since it is the disease that most commonly presents with lung involvement. The tests were also performed in patients with other diagnosis who had pulmonary symptoms or aggravation of the underlying disease.

	SLE n=35	JDM n=16	SSc n=7	LS n=6	MCTD n=8	TOTAL n=72
Unilateral PE N (%)	6 (17)	1 (6)	0	0	1 (12)	8 (11)
Bilateral PE N (%)	5 (14)	0	0	0	0	5 (7)
Pneumonitis N (%)	5 (14)	1 (6)	2 (29)	0	1 (12)	9 (12)
Nodules N (%)	5 (14)	0	0	1 (17)	1 (12)	7 (10)
Air trapping N (%)	3 (9)	0	2 (29)	1 (17)	0	8 (11)
Vessel wall thickening N (%)	2 (6)	0	0	0	0	3 (4)
Consolidation / Opacity N (%)	4 (12)	1 (6)	2 (29)	1 (17)	0	8 (11)
Ground glass opacities N (%)	5 (14)	4 (25)	5 (71)	0	0	16 (22)
Pulmonary hemorrhage N (%)	2 (6)	0	0	0	0	2 (3)
Fibrosis N (%)	1 (3)	3 (19)	1 (14)	0	1 (12)	5 (7)
Parenchymal bands N (%)	1 (3)	0	0	0	0	1 (1)
Pulmonary embolus N (%)	2 (6)	0	0	0	0	2 (3)
Calcinosis N (%)	0	1 (6)	0	0	0	1 (1)
Pleural thickening N (%)	1 (3)	0	0	0	1 (12)	2 (3)
Pulmonary hypertension N (%)	0	0	0	0	1 (12)	1 (1)
Infection N (%)	2 (6)	0	0	1(17)	0	3 (4)

Table 3: Abnormalities in chest HRCT.

Sixty-four patients were submitted to CXR during outpatient treatment due to an upper or lower respiratory infection. Patients who

did not have any pulmonary symptoms, neither aggravation of the underlying disease, were not submitted to pulmonary tests.

From the total sample of patients, 37% (72) had some degree of pulmonary involvement in at least one of the tests. The groups with higher pulmonary involvement were SSc (100%) and MCTD (46%). Patients with SLE and JDM had similar results, with pulmonary involvement in 35% of them. LS patients had the lowest rate of lower respiratory system involvement, with 25% of patients affected. All abnormalities found in the tests performed are described in Tables 2, 3, and 4.

From the 134 patients who were submitted to CXR, 58 had abnormal results. The main findings were unilateral or bilateral pleural effusion, opacities and infection. SLE patients were those who had more abnormalities, as shown in Table 2. Patients with scleroderma in general did not present any abnormalities in this test. Regarding JDM and MCTD, 24% and 46% of patients, respectively, had some abnormality on CXR.

Forty-five of 72 patients who were submitted to a chest CT had abnormal results. Again the SLE group presented the most varied manifestations. However, in contrast to the results presented on CXR, patients with SSc had several abnormal results as shown in Table 3. Two patients with LS, 7 with JDM and 3 with MCTD also presented with pulmonary involvement in their tests.

Only 27 patients underwent PFTs. In 7 of these, respiratory disorders were.detected, as shown in Table 4. Only the LS group had no patients with abnormal lung function

	SLE n=5	JDM n=7	SSc n=7	LS n=4	MCTD n=4	TOTAL n=27
Obstructive VD N (%)	1 (20)	1 (14)	2 (29)	0	1 (25)	5 (18)
Restrictive VD N(%)	1 (20)	1 (14)	2 (29)	0	0	4 (15)

Table 4 : Abnormalities in PFTs.

When comparing the groups with and without lung impairment-72 and 121 patients, respectively, they did not differ in relation to gender (p=0.192) and average age at diagnosis (p=0.615).

Discussion

In this study we observed pulmonary manifestations in 37% of patients with rheumatologic diseases. In a quarter of cases, the pulmonary involvement presented as infections, associated with immunosuppression (secondary to the disease itself or to treatment). In the remaining three quarters, pulmonary involvement was associated with the underlying disease itself.

Interestingly, only half of patients with some degree of pulmonary involvement had symptoms, which shows that the pulmonary manifestations may be present even before the clinical symptoms present [3,9]. Therefore, the systematic investigation of patients with diseases known to cause lung damage should be precocious. The most sensitive and specific method for detection of pulmonary involvement is the chest HRCT, which is able to show abnormalities even when CXR and PFTs are normal [19,20,26-28].

In SLE, pulmonary manifestations may arise during onset of the disease or during its course [10-14]. Both in adults and in children, the most common manifestation is pleurisy, accompanied in most cases by unilateral or bilateral pleural effusion, and this finding occurs in about 50% to 80% of adults and 5 to 67% of children [3,10-14]. In this study, pleural effusion occurred in 16% of patients.

In Scleroderma pulmonary involvement is one of the most common findings of the disease. It is mainly present in the systemic form of scleroderma, but may also occur in localized (linear) disease [3]. Pulmonary fibrosis is observed in up to 90% of the chest HRCTs in adults, and is the most common cause of restrictive ventilatory defects found in PFTs [19,20]. Pulmonary hypertension occurs in most cases, and is largely responsible for the high mortality of this disease [6,16-18]. This study showed exactly what literature reports, since 100% of SSc patients had alterations in the chest HRCT. It is interesting to note that CXR was not a good method to evaluate these patients, since only one child in this group had an abnormal result. In the group of LS, the number of patients who presented chest HRTC abnormalities was much lower (25%). This result, however, shows that even a localized disease can present with some kind of organ involvement [3]. Health professionals should be alert to this possibility in order to make an early diagnosis.

According to the literature, pulmonary involvement in JDM is rare, although it can occur in 30% to 50% of adults with DM [1,3,21-23]. In this study we found pulmonary involvement in 35% of JDM patients, however, about half of patients had an infection as the reason of pulmonary involvement. Our findings suggest that a proportion of children and adolescents with JDM might be underdiagnosed in relation to pulmonary damage caused by this disorder.

Up to 66% of adults with MCTD have interstitial lung disease and about 33% develop pulmonary hypertension, which are the most common pulmonary manifestations in this disorder [24,25]. In pediatric patients these rates are a little lower. In our study, only 3 patients had pulmonary involvement, with a wide-ranging spectrum of presentations.

Our study had some limitations: only symptomatic patients were submitted to tests, introducing a selection bias, this was a retrospective study, and only few patients performed pulmonary function tests.

As showed in this study, pulmonary involvement often occurs in rheumatic diseases, by the disease itself, as a result of immunosuppression caused by treatment, or even by the effects of the drugs themselves in this organ [1-4]. Periodic monitoring is mandatory in these patients, with history and physical examination, in order to assist the health professional to decide on the need for additional pulmonary investigation. The gold standard is the chest HRCT, because of its high sensitivity and specificity to detect pulmonary abnormalities [19,20,26-28]. This test, however, does not assess lung function. For this purpose, PFTs should be ordered. The CXR has significant limitations in detection of subtle alterations, presenting a considerable amount of false negatives [26-28]. There is a variety of pulmonary manifestations in the rheumatic diseases and there are no pathognomonic signs of pulmonary disease in each [1,5,7]. Because of the frequency and possible severity of the pulmonary involvement, patients should be investigated for it, in order to detect it early and start appropriate treatment to improve patient outcomes.

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