Concise report

Pulmonary function and autoantibodies in a long-term follow-up of juvenile dermatomyositis patients

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Abstract

Objectives. Pulmonary disease is a rare complication in JDM, described in only a few studies. This long-term follow-up study aimed to (i) describe pulmonary involvement in a national cohort of JDM patients estimated by conventional spirometry, (ii) compare pulmonary impairment with overall JDM outcome, and (iii) identify possible associations between pulmonary impairment and myositis-specific autoantibodies (MSAs).

Methods. Fifty-one JDM patients performed conventional spirometry in a cross-sectional follow-up study. The scores of the Myositis Damage Index (MDI), Myositis Damage by visual analogue scale (MYODAM-VAS) and physician’s global damage assessment were used to estimate JDM outcome. ANAs, MSAs and myositis-associated autoantibodies were analysed in all patients.

Results. Forty-two patients (82%) (mean follow-up time 14.3 years) had normal lung function. Four patients (8%) were diagnosed with JDM-related restrictive interstitial lung disease. No patients reported pulmonary symptoms. Patients with restrictive pulmonary function had increased long-term damage estimated by MDI ($P=0.008$), MYODAM-VAS ($P=0.04$), global assessment ($P=0.03$) and number of organ systems involved ($P=0.009$). We found significant correlation between the restrictive pulmonary function test and damage by the MDI ($r=0.43$, $P=0.003$), MYODAM-VAS ($r=0.44$, $P=0.002$), and global damage assessment ($r=0.43$, $P=0.003$). No association was found between the restrictive pulmonary function test and autoantibodies.

Conclusion. In a long-term follow-up study of JDM patients, the majority of patients demonstrated normal lung function. However, restrictive pulmonary impairment was identified in 8% of patients, indicating a need for repetitive pulmonary follow-up in JDM patients. Restrictive pulmonary involvement was associated with increased long-term JDM damage.

Key words: juvenile dermatomyositis, follow-up, pulmonary damage, myositis-specific autoantibodies, myositis-associated autoantibodies.

Introduction

JDM is a chronic inflammatory disease in childhood involving striated muscle and skin in affected patients [1]. Pulmonary involvement is a rare but well-known complication in JDM that is mainly associated with interstitial lung disease (ILD) [2, 3]. Restrictive pulmonary disease or ILD has been reported with frequencies ranging from 18.8 to 50% of children with JDM [2, 4–6]. A correlation between pulmonary fibrosis and Jo-1 autoantibodies in patients with dermatomyositis has been demonstrated [7, 8].
The aim of this study was to assess pulmonary function using spirometry in a long-term follow-up of JDM patients. Additionally, the study aimed to compare restrictive pulmonary impairment with overall JDM outcome and with myositis-specific and myositis-associated autoantibodies (MSAs and MAAs).

**Methods**

The study was a cross-sectional follow-up study. Patients were identified from the National Patient Register in Denmark (1976–2007). Patients were included if they fulfilled the Peter and Bohan criteria of definite and probable JDM [9, 10] and met the specific criteria required to take a lung function measurement test according to published guidelines [11].

**Pulmonary impairment and lung function measurements**

A conventional spirometry test was performed (Jäeger, Würzburg, Germany) in accordance with guidelines [11]. Forced expiratory volume in 1 s (FEV$_1$) and forced vital capacity (FVC) were calculated. Normal lung function was defined as an FEV$_1$ and FVC z-score $> -1.64$ (= lower normal limit) according to reference values adjusted for age, gender and height [12]. Reversibility to β-2 agonist was assessed only in cases with signs of obstructive lung function (FEV$_1$/FVC z-score $> -1.64$ or a ratio $< 0.8$). Significant reversibility was defined as a $> 12\%$ increase in FEV$_1$ after β-2 agonist. Pulmonary impairment was defined as lung function below normal values or radiological abnormalities compatible with ILD.

Indication of restrictive pulmonary disease was defined as pulmonary function tests with an FEV$_1$ and/or FVC z-score $> -1.64$ and no signs of airway obstruction (normal FEV$_1$/FVC z-score $> -1.64$ or a ratio $> 0.8$) at the time of follow-up or recent/previous chest high-resolution CT (HRCT) abnormalities compatible with ILD.

**JDM outcomes**

Validated score tools were used to estimate JDM outcome. Disease activity was measured using the JDM DAS, a tool that evaluates symptoms in skin and muscle [13]. Disease damage was measured by the Myositis Damage Index (MDI) and the Myositis Disease Damage by visual analogue scale (MYODAM-VAS) [14, 15], which assesses damage in nine organ systems: muscle, skeletal, cutaneous, gastrointestinal, pulmonary, cardiac, peripheral vascular, endocrine and ocular.

**Myositis autoantibodies**

MSAs (EJ, Jo-1, Mi-2, OJ, PL-12, PL-7 and SRP) and MAAs in patient serum were quantified in the Euroline Myositis Profile 3 immuno line blot by densitometric measurement in accordance with the manufacturer’s instructions (Euroimmun, Lübeck, Germany).

Jo-1 autoantibodies were also detected by ELISA according to the manufacturer’s instructions (Euroimmun, Lübeck, Germany). The patient serum samples diluted 1:160 were analysed for the presence of ANA on Hep-2 slides (ImmunoConcept, Sacramento, CA, USA) by indirect immunofluorescence.

**Ethics**

Approval was obtained from the Regional Committee on Health Research Ethics, Zealand (reference number SJ-69) and informed consent from the patients was obtained. All participants also gave informed consent to receive information concerning their own health. In cases where examination revealed findings that needed to be followed up, the participants were informed by the investigator and referred to an appropriate specialist.

**Statistics**

Standard methods were applied [16]. Data are presented as median (range) or mean (±SD). Differences in distributions were tested using chi-square or Fisher’s exact test or the Mann–Whitney U-test as appropriate. Correlations were calculated using Spearman’s rank correlation coefficient. MDI and MYODAM-VAS scores without the pulmonary elements were used when comparing patients with and without pulmonary involvement and for the correlation analyses. Level of significance was 5%. SPSS statistics software, version 17.0, was used for the statistical calculations (IBM, Armonk, NY, USA).

**Results**

A total of 71 patients fulfilled the criteria of JDM. Of these, three died due to JDM, nine were lost to follow-up and two were excluded due to other diseases (mental illness and liver transplant due to autoimmune hepatitis). Thus 57 patients were contacted and 52 (91%) agreed to participate in the study; however, 1 child was too young to cooperate. Consequently, 51 patients (37 females, 14 males) performed spirometry at a mean of 14.3 years after disease onset (range 2–36 years) (Table 1).

At the time of follow-up, 42 patients (82%) had normal lung function. A diagnosis of ILD was made in four patients (8%): reduced restrictive lung function was demonstrated in two patients at follow-up, whereas two other patients had previously been diagnosed with ILD by chest HRCT. The characteristics of the JDM patients with ILD are displayed in Table 2. At follow-up, two patients were still receiving treatment for active, chronic JDM (patients 2 and 4) and two patients (patients 1 and 3) were in complete remission and off medication. All four patients had definite JDM according to the Peter and Bohan criteria. An obstructive lung function pattern was seen in seven patients (14%), of whom four had a positive reversibility for β-2 agonist. None of the patients in the cohort reported any pulmonary symptoms.

The deceased patients were females, ages 5, 7 and 10 years. They died 3, 18 and 22 months after disease onset, respectively. One died from a cerebral insult and two from fulminant mucosal bleeding episodes. One patient had interstitial pulmonary disease at disease onset, but normal pulmonary status (assessed by HRCT) when she
died. The other deceased patients had no pulmonary involvement.

At follow-up, the patients with a restrictive pulmonary function test had increased long-term damage compared with patients whose pulmonary function test was either normal or obstructive, estimated by cumulated MDI ($P = 0.008$) and MYODAM-VAS ($P = 0.04$) (Table 1). In a correlation analysis, signs of restrictive pulmonary involvement were positively correlated with (i) disease activity estimated by JDM-DAS ($r = 0.34$, $P = 0.02$), (ii) damage estimated by MDI ($r = 0.43$, $P = 0.003$), MYODAM-VAS ($r = 0.44$, $P = 0.002$) and physician’s global assessment ($r = 0.43$, $P = 0.003$).

ELISA and immuno line blot both demonstrated that all patients were anti-Jo-1 negative. Immuno line blot showed that all patients were also negative for Ku-, SRP, EJ, OJ, PL-7 and PL-12 autoantibodies. There were no significant differences in ANA or other autoantibodies between patients with and without pulmonary changes (Table 1).

**Discussion**

We present one of the longest follow-up studies of JDM patients from a national cohort describing pulmonary involvement in relation to cumulative organ damage, disease activity and myositis-related autoantibodies. Mean follow-up time was 14.3 years and 82% of patients revealed lung function within the normal range. We found that 8% of JDM patients had restricted pulmonary function as assessed by spirometry or HRCT, supporting recent follow-up studies that report pulmonary involvement in 3–6% of patients 60 months–16.8 years after disease onset [6, 15, 17].

In a previous medical records review of 57 JDM patients in Denmark, we found pulmonary involvement in 12% of the patients (mean follow-up time 7 years) [18]; 75% of the patients in the present study were also included in our previous study. Of the nine patients with pulmonary involvement in the medical records review, seven patients (80%) also participated in the present study: one (patient 3) had ongoing pulmonary involvement, one died due to JDM but had no pulmonary involvement at the time of death and one was lost to follow-up. In the present study (mean follow-up time 14.3 years) we found decreased pulmonary function in 8% of patients. As the cohorts are small and not quite identical, they cannot be compared. Nonetheless, the results indicate that pulmonary involvement might decrease over time.

**Table 1** Characteristics of two groups of JDM patients evaluated for restrictive pulmonary disease

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>JDM patients without restrictive lung disease</th>
<th>JDM patients with restrictive lung disease</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with definite JDM type, n (%)</td>
<td>47</td>
<td>4</td>
<td>0.14</td>
</tr>
<tr>
<td>Patients in remission, n (%)</td>
<td>39 (82.9)</td>
<td>2 (50)</td>
<td>0.32</td>
</tr>
<tr>
<td>Age, mean (s.d.) (range), years</td>
<td>21.7 (11.1) (4.2–45.9)</td>
<td>14.2 (4.4) (10.0–19.7)</td>
<td>0.3</td>
</tr>
<tr>
<td>Age at disease onset, mean (s.d.) (range), years</td>
<td>7.7 (4.7) (1.4–17.8)</td>
<td>7.7 (4.2) (1.5–10.5)</td>
<td>0.3</td>
</tr>
<tr>
<td>Disease duration, mean (s.d.) (range), years</td>
<td>4.2 (2.9) (0.6–10.6)</td>
<td>5.3 (2.5) (2.6–8.5)</td>
<td>0.3</td>
</tr>
<tr>
<td>Follow-up time, mean (s.d.) (range), years</td>
<td>14.3 (10.7) (1.1–35.1)</td>
<td>6.5 (3.0) (2.6–9.2)</td>
<td>0.3</td>
</tr>
<tr>
<td>Diagnostic delay, mean (s.d.) (range), years</td>
<td>0.7 (1.0) (0.1–0.7)</td>
<td>0.3 (0.1) (0.2–0.4)</td>
<td>0.3</td>
</tr>
<tr>
<td>JDM DAS, mean (s.d.) (range)</td>
<td>1.5 (2.0) (0–7)</td>
<td>7.3 (6.4) (1–15)</td>
<td>0.02</td>
</tr>
<tr>
<td>FEV1 % predicted/z-score, mean (s.d.)</td>
<td>100.9 (12.8)/0.43 (1.0)</td>
<td>74.1 (9.4)/−2.1 (1.2)</td>
<td>0.007</td>
</tr>
<tr>
<td>FVC % predicted/z-score, mean (s.d.)</td>
<td>109.7 (15.0)/0.35 (1.0)</td>
<td>76.0 (11.4)/−2.5 (1.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>FEV1/FVC ratio, mean (s.d.)</td>
<td>1.0 (0.07)</td>
<td>1.0 (0.08)</td>
<td>0.9</td>
</tr>
<tr>
<td>MDI score, mean (s.d.) (range)</td>
<td>1.7 (2.1) (0–7)</td>
<td>10.5 (7.9) (3–21)</td>
<td>0.008</td>
</tr>
<tr>
<td>MYODAM VAS score, mean (s.d.) (range)</td>
<td>1.5 (2.6) (0–19.5)</td>
<td>14.9 (11.5) (2.2–29.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Physician’s global assessment, mean (s.d.) (range)</td>
<td>1.1 (1.6) (0–5.2)</td>
<td>4.7 (2.9) (2–7.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Number of organ systems involved, mean (s.d.) (range)</td>
<td>1.1 (1.3) (0–4)</td>
<td>4.8 (2.2) (2–7)</td>
<td>0.009</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>3 (6.4)</td>
<td>0 (0)</td>
<td>—</td>
</tr>
<tr>
<td>Ex-smokers, n (%)</td>
<td>2 (4.3)</td>
<td>0 (0)</td>
<td>—</td>
</tr>
<tr>
<td>Autoantibodies, n (%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
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</tbody>
</table>

Mi-2 | 1 (2) | 0 (0) | 0.92 |
PM-Scl75 | 2 (4) | 1 (25) | 0.22 |
PM-Scl100 | 1 (2) | 1 (25) | 0.15 |
Ro-52 | 3 (6) | 0 (0) | 0.78 |
ANA | 14 (30) | 2 (50) | 0.37 |
EJ, Jo-1, OJ, PL-12, PL-7, SRP, Ku | 0 | 0 | — |

JDM DAS: Juvenile Dermatomyositis Disease Activity; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; MDI: Myositis Damage Index; MYODAM VAS: Myositis Damage Visual Analogue Scale. a Patients with normal lung function test or obstructive pattern. b Mann–Whitney rank sum test unless otherwise stated. c Fisher’s exact test. d Remission is defined as free of medication and symptoms for at least 1 year. e MDI and MYODAM scores are without the pulmonary scores.
Our cohort was divided into two subgroups (normal lung function and restrictive pulmonary impairment) for further analysis, as restrictive pulmonary changes are a well-known complication of JDM [3]. An obstructive lung function pattern compatible with asthma (14% of patients) was assumed not to be related to JDM disease.

Overall, the group identified as exhibiting functional markers of restrictive pulmonary impairment had a more severe disease course with significantly higher cumulated MDI, MYODAM-VAS and global damage scores. Moreover, significantly more organ systems were affected in these patients. This indicates that pulmonary involvement is demonstrated in JDM patients with more systemic involvement, as shown by Sanner et al. [6], who described increased pulmonary abnormalities on HRCT associated with cumulative organ damage.

Furthermore, the degree of disease activity was significantly higher in the group of patients who completed a restrictive pulmonary function test. This confirms previous findings that show that pulmonary changes occur early in the disease course and that the lungs become a target organ when the disease is active [4].

We did not demonstrate any association to ANA or other autoantibodies between patients with and without pulmonary changes. The presence of autoantibodies against aminoacyl-transfer RNA synthetases (ARSs), including Jo-1, has been described to be associated with or even to be a marker for the development of ILD in adults with polymyositis or dermatomyositis [19]. In accordance with several other studies, we found no autoantibodies against Jo-1 or other ARSs in the JDM cohort [20, 21], whereas Rider et al. [7] found Jo-1 and PL-7 autoantibodies in a small number of JDM patients. Wedderburn et al. [8] found Jo-1 autoantibodies in 2 of 27 patients with JDM-systemic sclerosis overlap syndrome, but found neither Jo-1 nor other ARS autoantibodies in patients with classical JDM. We detected Mi-2 autoantibodies in 1 of the 51 investigated patients (2%); other authors have reported the presence of these autoantibodies in 5–17% of JDM patients [7, 8, 20]. This discrepancy in the frequency of autoantibodies could be due to the intercohort differences of the investigated JDM populations or the use of different methods for autoantibody detection. The immuno line blot from Euroimmun has been validated by other investigators [21, 22]. We used both ELISA and immuno line blot methods for the detection of Jo-1 autoantibodies, but we cannot rule out the possibility that we would have found Jo-1 autoantibodies or a higher frequency of Mi-2 autoantibodies if we had used another more sensitive assay. However, previous studies that have used ELISA [8] as well as the more conventional methods of immunodiffusion and radioimmunoprecipitation [8, 20] for antibody detection also did not detect Jo-1 autoantibodies in their JDM cohorts, and therefore we consider our results reliable.

The strength of our study is the close clinical evaluation and data reliability at follow-up. Furthermore, the inclusion of patients from the National Patient Register enabled us to include a broad spectrum of JDM patients, including...
patients who are not followed at tertiary units. The study is limited by the relatively small sample size, especially in the group of patients with pulmonary involvement, and this gives rise to a risk of type 2 errors. This was not a blinded study, and thus bias may have been introduced in the physician’s global assessment score. Furthermore, due to the nature of cross-sectional follow-up studies, these studies only enable clarification of issues to be investigated in prospective long-term follow-up studies. Finally, present measurement of lung function might not reveal the occurrence of previous, more severe pulmonary impairment. This was the case in two of the ILD patients who had demonstrated a restrictive flow volume curve earlier, but had improved their lung function into the normal range at the time of follow-up. The study would have been improved by use of the standard measurements in the diagnosis and evaluation of restrictive lung disease, diffusion capacity and total lung capacity. However, our findings from the conventional spirometry were supported by CT scans that demonstrated signs of ILD in the majority of the affected patients.

Although the majority of patients demonstrated normal lung function without pulmonary complaints, this study highlights the importance of identifying patients with pulmonary symptoms at disease onset. Moreover, it also highlights the importance of performing repetitive pulmonary function measurements and imaging, such as chest HRCT, since subclinical pulmonary impairment seems to be associated with more severe disease course [6]. Further studies are needed to document whether early, relevant and aggressive treatment can improve the pulmonary outcome or even prevent pulmonary damage in patients with JDM.

Rheumatology key messages

- In a 14-year follow-up study of 51 JDM patients, 8% demonstrated decreased spirometric pulmonary function with a restrictive pattern.
- Pulmonary involvement was significantly associated with increased long-term JDM damage.

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References

