Pulmonary manifestations and progression of lung disease in juvenile onset mixed connective tissue disease

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ABSTRACT

Objective. To assess the occurrence and extent of interstitial lung disease (ILD) in patients with juvenile mixed connective tissue disease (JMCTD), compare pulmonary function in patients and matched controls, explore associations between ILD and disease-related variables, and examine progression of pulmonary manifestations over time.

Methods. A cohort of 52 JMCTD patients were examined in a cross-sectional study after mean 16.2 (SD 10.3) years disease duration with high-resolution computed tomography (HRCT) and pulmonary function tests (PFTs) comprising spirometry, diffusion capacity of carbon monoxide (DLCO) and total lung capacity (TLC). Matched controls were examined with PFTs. Previous HRCT and PFTs were available in 37 and 38 patients, respectively; mean 8.8 and 10.3 years before study inclusion.

Results. Compared to controls, JMCTD patients had lower forced vital capacity (FVC), DLCO, and TLC (p<0.01). The most frequent abnormal PFT was DLCO in 67% of patients *vs*. 17% of controls (p<0.01). Fourteen patients (27%) had ILD on HRCT. Most had ILD in <10% of their lungs. ILD was associated

with low values for FVC and TLC, but not with DLCO. HRCT findings did not progress significantly over time, but FVC declined (p<0.01).

Conclusions. Compared to controls, JMCTD patients had impaired pulmonary function. ILD was present in 27% of patients after mean 16 years of disease duration, mostly as mild disease, and did not progress. ILD seems to be less common in juvenile than in adult-onset MCTD, and ILD in JMCTD seems mostly mild and stable over time.

Key index terms: mixed connective tissue disease, interstitial lung disease, pulmonary fibrosis, paediatric rheumatology, autoantibodies, outcome research

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INTRODUCTION

Mixed connective tissue disease (MCTD) is a rare autoimmune disease characterised by serum autoantibodies directed against ribonucleoprotein (anti-RNP), and with clinical findings that include Raynaud phenomenon, puffy hands, as well as features of systemic sclerosis (SSc), systemic lupus erythematosus (SLE) and/or polymyositis.

According to the diagnostic criteria for MCTD described by Kasukawa and colleagues, pulmonary manifestations comprise pulmonary fibrosis, restrictive lunge disease (vital capacity (VC) <80% of predicted) and/or reduced diffusion capacity of carbon monoxide (DLCO) <70% of predicted (1). In adult MCTD, the prevalence of pulmonary manifestations, particularly interstitial lung disease (ILD), has been found to range from 35% to 78%, and to represent a major cause of morbidity and mortality (2-7). The prognosis in MCTD seems to vary from mild disease, as initially described by Sharp et al. (8), to a disease with severe complications, such as pulmonary fibrosis and pulmonary arterial hypertension (4, 9).

Disease onset during childhood or adolescence (before 18 years of age) has been reported to occur in 7−23% of all MCTD cases (10, 11). Data on lung involvement in juvenile MCTD are scarce. Aaløkken et al. (12) found evidence of ILD in 25% of 24 patients with juvenile MCTD, mostly as very mild disease. Further, Mier et al. (13) described ILD in three of ten patients in a subpopulation believed to be at risk. The prevalence and extent of ILD observed in juvenile MCTD was lower than that reported in most studies on adult MCTD (2-7). Progression of lung disease in adult onset MCTD has been shown to be modest (3, 6). Nevertheless, studies focusing on the long-term outcome of pulmonary manifestations in patients with juvenile MCTD are lacking.

Retrospective, small studies on juvenile MCTD have described reduced DLCO in 15–42%, and restrictive lung disease in 24–64% of patients (13-15). However, no research team has compared pulmonary function with controls from a general population. Whether there is a relationship between pulmonary function, ILD and other disease-related variables in juvenile MCTD is not known.

Herein, we aimed to: (i) examine and assess the occurrence and extent of ILD in juvenile MCTD in a representative nationwide cohort; (ii) compare pulmonary function in patients with juvenile MCTD with age- and sex-matched controls from a general population; (iii) examine ILD progression and changes in pulmonary function over time; (iv) evaluate possible associations between pulmonary findings and disease-related variables.

METHODS

Patients and controls

The current cross-sectional study was performed at Oslo University Hospital (OUH) from March 2013 to June 2015.

Inclusion criteria were: fulfilment of the criteria for the diagnosis of MCTD set by Kasukawa and colleagues (1) or Alarcón-Segovia and Villareal; (16) symptom onset before the age of 18 years; *and* a clinical diagnosis of MCTD confirmed by a rheumatologist or paediatrician. Patients were identified through multiple acquisition routes and a nationwide approach, identification and inclusion have been described in detail previously (17). Sixty two patients were initially identified, of these patients three were deceased, three did not wish to participate, one did not respond to our enquiries, and three had developed clinical SLE and

were excluded. Thus, 52 patients with juvenile MCTD comprised our study population. Controls matched for age and sex were selected randomly from the Norwegian population register. Controls with a history of autoimmune disease necessitating immunosuppressive medication, heart disease and/or lung disease (other than mild asthma) were excluded. Informed consent was obtained from all participants and the parents of patients and controls <16 years old, according to the *Declaration of Helsinki*. The study protocol was approved by the Regional Ethics Committee for Medical Research (2012/1721).

Clinical data

Patients and controls underwent a thorough clinical examination undertaken by the main investigators (SOH or VL). Clinical parameters during the entire disease course and upon examination were obtained from medical records and patient interviews. Through examination of medical records and available data from a former study done by our research team (12), previous HRCT images (Time 1) were available in 37 patients from at least 2 years before the cross sectional examination (Time 2), and previous PFTs were available in 38 patients. The mean time-span between the first HRCT and the second HRCT was 8.3 years (SD 2.7), and for the PFTs it was 10.3 years (SD 1.0). Smoking habits and level of physical activity were obtained from questionnaires.

Acquisition and analyses of CT images

HRCT was undertaken in patients only, and obtained in the supine position, during deep inspiration and breath-hold. Images were reconstructed in sections of thickness measuring

1–1.25 mm with 10-mm intervals and at sections of thickness measuring 2.5 mm reformatted in the axial, coronal, and sagittal planes. The images were reviewed by two experienced chest radiologists blinded to clinical information on a Picture Archiving and Communication System (PACS). The presence, extent and distribution of ILD was evaluated according to the CT criteria of ILD recommended by The Nomenclature Committee of the Fleischner Society (18). These criteria comprised reticular pattern (i.e., the coarseness of fibrosis), ground-glass opacities, traction bronchiectasis, interlobular septal thickening, and airspace consolidations. The reticular pattern was classified into three grades: 1 (fine intralobular fibrosis without evident cysts); 2 (mostly microcystic reticular pattern involving air spaces ≤4 mm in diameter); 3 (a predominantly macrocystic reticular pattern with air spaces >4 mm in diameter). HRCT findings were reviewed in four zones divided in a craniocaudal manner by the aortic arch, carina, and inferior pulmonary veins. The extent of fibrosis was expressed as a percentage of the TLV. Area measurements were done precisely by drawing a freehand region of interest on the PACS screen.

Pulmonary function tests

All patients and controls performed PFTs according to a standardized protocol and guidelines set by the American Thoracic Society/European Respiratory Society (ATS/ERS) (19, 20) and included spirometry, determination of static lung volumes and gas diffusing capacity. All measurements were made using an automated V_{max} V6200 system (VIASYS Respiratory Care, Yorba Linda, CA, USA). Recorded variables were forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), total lung capacity (TLC), DLCO, and DLCO divided by alveolar volume (VA). The values were recorded in absolute terms and as the percentage of the predicted value. Predicted values were derived from reference equations for each sex, with age and

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height as predictor variables. Low values for FVC, FEV1, DLCO and TLC were defined as <80% of predicted; a low value for FEV1/FVC was defined as <0.70. These cut-off points correspond to the lower 5th percentiles in reference material, and are in accordance with ERS recommendations (21).

Six-minute walk test (6MWT)

The 6MWT was carried out on a straight indoor line measuring 35 m according to ATS guidelines (22) All participants scored their level of exhaustion on a modified Borg scale (23) using values from 0 (no dyspnoea) to 10 (maximal exhaustion).

Statistical analyses

Differences between patients and controls, and between patients at Time 1 and Time 2, were tested with the paired-samples *t*-test for continuous, normally distributed variables, Wilcoxon's rank sum test for non-normally distributed variables, and McNemar's test for categorical variables. To test differences between patients with and without ILD, we used the independent samples *t*-test for continuous normally distributed variables, Mann–Whitney *U*-test for non-normally distributed variables, and the χ^2 test or Fisher's exact test was used to test differences in categorical variables. Correlations between extent of ILD, DLCO and FVC were determined by the Spearman correlation coefficient. To identify factors associated with ILD, we undertook univariable logistic regression analyses on disease-related variables from the time of diagnosis. Statistical analyses were undertaken with SPSS v22.0 (IBM, Armonk, NY, USA).

RESULTS

The patients were mean 28.0 (SD 10.3) years upon examination (median 27.4; range 11.8–53.8 years) and had a median duration of disease of 15.7 (range 0.6–41.2) years from symptom onset (Table 1). The controls were mean 29.0 (SD 10.2) years.

Compared with controls, patients were shorter (166.0 *vs.* 170.1 cm, p =0.016), and had a lower body weight (63.0 *vs.* 68.1 kg, p =0.033). Patients and controls reported a similar amount of physical activity and smoking habits. Two patients reported dyspnoea upon exertion, one of whom had coronary artery disease. None of the controls reported pulmonary symptoms.

Pulmonary function in patients and controls

PFT values were impaired in 69% of the juvenile MCTD patients and 25% of controls (p<0.001) (Table 2). The most commonly impaired PFT was DLCO (low in 67% of patients and 17% of controls, p<0.001). FVC was impaired in 21% of patients and zero controls (p < 0.001). TLC was impaired in 12% of patients and zero controls (p =0.009). Patients walked a mean 65 meters shorter on 6MWT than controls (p =0.002). PFTs and the 6MWT remained significantly lower in patients than in their matched controls even after excluding patients with ILD on HRCT (data not shown).

HRCT findings in patients

Fourteen patients (27%) had ILD on HRCT (reticular pattern, ground-glass attenuation, interlobular septal thickening, airspace consolidations and/or traction bronchiectasis) (Table 3). The most common abnormality was a reticular pattern, which was present in 13 patients (25%).

The extent of ILD was a median of 4% (range 1–75%) of the lung volume. Most (11/14) cases showed involvement of ≤10% of TLV (Figure 1). The remaining three patients had 12%, 18% and 75% of the lung parenchyma affected, respectively. Of the 14 patients with ILD, only the patient with 75% involvement of the lung reported pulmonary symptoms (dyspnoea upon exertion).

A reticular pattern was most often found in the basal lung zone (11/14 patients, 79%). Seven of 14 (47%) cases had findings between the inferior pulmonary veins and the level of the carina, 6/14 (40%) between the level of the carina and aortic arch, and 3/14 (20%) above the aortic arch.

Associations between ILD and patient characteristics, disease variables and PFTs

A higher proportion of patients with ILD had low FVC (43% *vs*. 14%, p =0.023) and low TLC (36% *vs*. 3%, p =0.002) compared with those without ILD (Table 4). Patients without ILD had more often been treated with corticosteroids (90% *vs*. 64%, p = 0.033) and anti-malarial agents (92% *vs*. 57%, p = 0.003) than those with ILD. The use of corticosteroids (but not anti-malarial agents) correlated with SLE-like disease at the time of examination (r = 0.41, p =0.003). The extent of ILD correlated negatively with FVC%-predicted (ρ = −0.64, p =0.01) and DLCO%-predicted (ρ = −0.81, p <0.01) at Time 2, but not with other disease-related variables at the diagnosis or after a mean of 16 years (data not shown).

Progression of HRCT findings and changes in PFT values

Changes on HRCT and in PFT values in 37 and 38 patients, respectively, over a median of 8.3 and 10.3 years are shown in Table 5. Values of FVC and FEV1 declined significantly, but the DLCO was stable from Time 1 to Time 2. There was no significant increase in ILD findings

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with regard to the extent, presence or grade of the reticular pattern between Time 1 and Time 2.

DISCUSSION

In this long-term outcome study of 52 juvenile MCTD patients, we found ILD in 27% after mean disease duration of 16.2 years. Most cases had <10% of lung parenchyma involved. Compared with controls, patients had lower values for FVC, DLCO and TLC. ILD was associated with low values for FVC and TLC. No significant progression in ILD was observed over time. This is the first systematic case-control study on pulmonary manifestations, and the first to assess the presence and progression of ILD in an unselected cohort of juvenile MCTD patients.

The prevalence of ILD in adult MCTD has been reported to be 35–78% (2-7). Recently, Reiseter et al. observed ILD in 41% of 119 patients after a mean duration of disease of 16.5 years (3). In our cohort of juvenile MCTD cases, a lower prevalence of 27% of cases with ILD was noted even though our patients had a comparable long duration of disease. Two studies on juvenile MCTD have also reported the ILD prevalence to be in the lower range. Mier et al. (13) found pulmonary fibrosis on CT in 30% of 10 patients believed to be at risk of ILD. Aaløkken and colleagues reported a prevalence of ILD of 25% in 24 juvenile MCTD patients after a median duration of disease of 10.5 years (12). In juvenile SSc and dermatomyositis, the prevalence of ILD has been reported to be 21% and 14%, whereas in juvenile SLE, ILD rarely occurs(24-26). Thus, a prevalence of ILD of 27% in our study is in accordance with that reported in juvenile MCTD, but lower than that reported in most studies of adult MCTD patients. However, compared to other paediatric connective tissue diseases, ILD is a frequent finding in juvenile MCTD.

Most of our patients had mild fibrosis, and only 6% had lung involvement of >10%. These findings are in accordance with those reported by Aaløkken and colleagues in juvenile MCTD patients(12). With respect to adult MCTD, however, Reiseter et al. found a much higher proportion (17%) of cases with involvement of >10% of TLV(3). Furthermore, in a large cross-sectional study with 126 adult patients, Gunnarsson et al. reported that 19% of cases had severe fibrosis(2). According to our results, not only the prevalence, but also the severity of ILD in juvenile MCTD seems to be lower than that in adult MCTD.

Impaired lung function was found in 69% of our patients, and values of FVC, FEV1, DLCO and TLC were reduced significantly compared with those in controls. The most commonly impaired PFT was DLCO, which was noted in 65% of cases. However, on a group level, the reduction was only moderate. Patients with ILD and impaired PFTs were mainly asymptomatic; only one patient reported symptoms of ILD. The 6MWT was clearly reduced compared with that of controls, but within the expected normal range(27), which supported the notion that lung-function impairment in juvenile MCTD is common, but mostly mild. We believe that the somewhat unexpected finding that 25% of controls had abnormal PFTs could be explained by the fact that we did not use mild asthma and smoking as exclusion criteria.

Low values of FVC and TLC were associated significantly with ILD. In contrast, low DLCO was not associated with ILD even though it was the most commonly impaired PFT in juvenile MCTD. Abnormal DLCO has also been described to occur commonly in other types of connective-tissue disease in children. In a cohort of 60 juvenile patients with SLE, Lilleby et al. found a low DLCO in 35% and none of them had findings of ILD on HRCT(26). Furthermore, in juvenile dermatomyositis, Sanner et al. described low DLCO in half of 59

patients without association with ILD(25). Thus, in juvenile MCTD, low DLCO cannot be explained by restrictive lung disease alone, but may be due to other causes, such as pulmonary vascular disease(28) or structural changes in alveolar membranes(29). In addition, in SSc, fibrosis has been shown to be better predicted by FVC than by DLCO(30-33).

Our data showed no significant progression of ILD over a mean observation period of 8 years. In adult MCTD, Kawano-Durado et al.(6) found limited ILD progression over 10 years, with an increase in lower-lobe ILD score from 7.5 to 11.2%. Reiseter et al.(3) found modest progression of ILD in 19% of cases over 6.4 years, with an increase in median extension of ILD from 5% to 7%. The presence and extent of ILD are prognostic factors for increased mortality in MCTD(2, 3). Our data imply that ILD in juvenile MCTD is mostly stable over long-term disease duration, but we cannot exclude that mild ILD in these patients should be of concern, as lung function declined over time.

Patients without ILD after mean disease duration of 16 years had more often been treated with prednisolone and antimalarial agents than patients with ILD. Although we cannot make conclusions based on these associations due to the relatively small sample size and low number of patients with ILD, we believe that these are relationships that could be assessed in more depth in larger studies. We found no associations between ILD and disease activity measurements or smoking status. Reiseter and colleagues showed male sex, presence of anti-Ro52 antibodies, and a high level of anti-RNP antibodies to be predictors for ILD progression in adult MCTD(3), but none of these factors were associated with ILD in our cohort.

The present study had two main limitations. The first limitation was the small cohort of patients, and especially the results regarding the subgroup of patients with ILD should be

interpreted with caution, as these analyses are of more exploratory nature. However, compared with other relevant studies, our cohort was the largest cross-sectional study carried out on juvenile MCTD. Second, ideally we should have had data on all 52 patients also at Time 1, and we cannot exclude that the study was underpowered with regards to assessing ILD progression.

The main strength of our study was that it was the first to compare juvenile MCTD patients with a control group. It was also the largest study to assess HRCT and PFT systematically in all patients, and the cohort is believed to be representative of juvenile MCTD patients living in Norway, as described in more detail previously(17). Progression of pulmonary manifestations in juvenile MCTD patients has not previously been reported, and we had a long follow-up of 16.2 years from the diagnosis. All HRCTs, from Time 1 and Time 2, were examined by the same experienced radiologist using a standardised method.

In conclusion, this long-term study showed that compared to matched controls, juvenile MCTD patients had impaired pulmonary function. ILD was found in 27% of patients, mostly as mild disease. The presence and extent of ILD did not progress. These findings suggest that ILD is stable in juvenile MCTD, and that the progression and severity of ILD is less prevalent than that reported in adult onset MCTD. Our results may imply that asymptomatic juvenile MCTD patients with mild ILD can be followed with regular PFTs alone, but repeated HRCT should be considered in case of unexplained pulmonary symptoms or reduction in PTFs.

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Figure 1. HRCT abnormalities in juvenile MCTD.
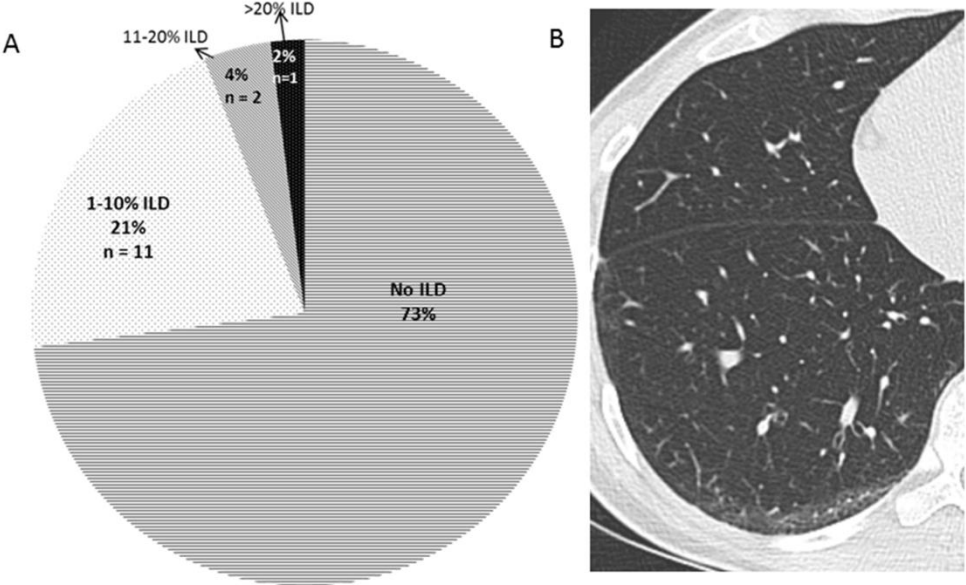
A. ILD extent in percent of total lung parenchyma. B. HRCT image of a typical patient with JMCTD, with a fine reticular pattern grade 1 and 2, and 7% of total lung volume involved.

Table 1 Characteristics in patients with juvenile mixed connective tissue disease and controls from the general population

Variable	JMCTD patients n = 52	Controls n = 52	p value
	n = 52	n = 52	
Age at onset, years	11.7 (3.1)	NA	
Age at diagnosis, years	14.4 (4.4)	NA	
Disease duration (from onset)	16.2 (10.3)	NA	
Female gender, n (%)	44 (85)	44 (85)	1.00
BMI, kg/m²	22.7 (3.5)	23.4 (3.0)	0.239
Height, cm	166.0 (7.5)	170.1 (8.5)	0.016
Weight, kg	63.0 (12.1)	68.1 (12.1)	0.033
Current smokers, n (%)	7 (14)	9 (17)	0.586
Never smokers, n (%)	35 (67)	34 (65)	0.832
Hemoglobin, g/100ml	13.5 (1.2)	13.6 (1.1)	0.809
Vigorous physical activity (hours/week)	2.0 (0-25)	2.0 (0-55)	0.400
Moderate physical activity (hours/week)	2.0 (0-28)	1.2 (0-30.0)	0.278

Values refer to the mean (SD) or median (min/max range) if not indicated otherwise
NA, not assessed; BMI, body mass index

Table 2 Pulmonary function after mean 16.2 years of disease duration in juvenile MCTD patients and controls

	Patients n = 52	Controls n = 52	Mean difference	*p* value
FVC, litres	3.4 (0.6)	4.3 (1.0)		<0.001
FVC%	89 (14.7)	109 (11.9)	20%	<0.001
FEV1, litres	2.9 (0.5)	3.5 (0.8)		<0.001
FEV1%	89 (13.7)	103 (11.0)	14%	<0.001
FEV1/FVC ratio	0.86 (0.06)	0.82 (0.07)		0.001
DLCO mmol/kPa	6.8 (1.3)	9.2 (2.4)		<0.001
DLCO%	73 (12.5)	94 (16.0)	21%	<0.001
DLCO/VA	1.6 (0.2)	1.8 (1.0)		0.282
DLCO/VA%	88 (12.7)	92 (13.4)	4%	0.207
TLC, litres	4.8 (1.0)	6.0 (1.2)		<0.001
TLC%	90 (13.1)	108 (10.6)	18%	<0.001
Abnormal PFT*	36 (69)	13 (25)		<0.001
FVC <80%, n (%)	11 (21)	0		<0.001
FEV1 <80%, n (%)	12 (23)	2 (4)		<0.001
FEV1/FVC <0.70, n (%)	1 (2)	3 (6)		0.617
DLCO <80%, n (%)	35 (67)	9 (17)		<0.001
DLCO <70%, n (%)	19 (37)	1 (2)		<0.001
DLCO/VA <80%, n (%)	12 (23)	8 (15)		0.338
TLC <80%, n (%)	6 (12)	0		0.009
6 MWT, meters	634.3 (76.5)	698.9 (86.6)		0.002
Borg CR10 scale	2.0 (0-4.0)	1.0 (0-3.0)		0.072

Values refer to the mean (SD) if not indicated otherwise

*FVC, FEV1 and/or DLCO <80% of expected value, and/or FVC/FEV1 < 70% of predicted

MCTD, mixed connective tissue disease; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; VC, vital capacity; DLCO, diffusion capacity of carbon monoxide; VA, alveolar volume; TLC, total lung capacity; PFT, pulmonary function tests; 6 MWT, 6 min walk test; CR10, category ratio

Table 3 HRCT findings in 52 juvenile MCTD
patients after mean 16.2 year disease duration

	n (%)
ILD on HRCT*	14 (27)
Ground glass attenuation	2 (4)
Reticular pattern present	13 (25)
Reticular pattern grade 1	12 (23)
Reticular pattern grade 2	6 (12)
Reticular pattern grade 3	1 (2)
Interlobular septal thickening	0
Airspace consolidations	0
Bronchiectasis	1 (2)

*Defined as reticular pattern and/or ground glass attenuation,
interlobular septal thickening, airspace consolidations and
bronchiectasis
HRCT, high resolution computed tomography; ILD, interstitial
lung disease

Table 4 Patient and disease characteristics in 52 patients with juvenile MCTD with and without interstitial lung disease after mean 16.2 years disease duration

Variable	No ILD n=38	ILD n=14	*p* value
Characteristics at examination			
Female gender, n (%)	34 (90)	10 (71)	NS
Age, years	27.1 (10.3)	30.4 (10.2)	NS
Disease duration (from symptom onset)	15.1 (10.2)	19.4 (10.2)	NS
BMI, kg/m²	23.3 (3.0)	23.7 (2.9)	NS
Current smokers, n (%)	3 (8)	4 (29)	NS
Never smokers, n (%)	26 (68)	9 (64)	NS
SLE-like disease, n (%)	22 (58)	5 (36)	NS
SSc-like disease, n (%)	22 (58)	14 (100)	0.025
PM-like disease, n (%)	2 (5)	0	NS
Pulmonary function			
Impaired PFT^, n (%)	27 (73)	9 (64)	NS
DLCO < 80%, n (%)	26 (70)	9 (64)	NS
DLCO <70%, n (%)	13 (34)	6 (43)	NS
FVC < 80%, n (%)	5 (14)	6 (43)	0.023
TLC <80%, n (%)	1 (3)	5 (36)	0.002
FEV1/FVC < 0.70 n (%)	1 (3)	0	NS
6MWT, meters	626.5 (77.1)	626.9 (79.8)	NS
Disease activity at examination			
Active disease, n (%)	26 (68)	9 (64)	NS
Number of active joints	0 (0-11)	0 (0-2)	NS
Anti-RNP, titre x10^3 U/L	83.5 (0-240)	234.0 (17-240)	NS
ESR, mm/hour	9.0 (2-54)	8.0 (2-30)	NS
CRP, mg/l	0.7 (0-15)	0.7 (0-9.3)	NS
Anti-Ro52 positive, n (%)	1 (3)	0	NS
PGA, 10 cm VAS	1.5 (0-58.0)	2.9 (0.2-5.7)	NS
Rodnan skin score	0 (0-4)	0 (0-11)	NS

Values refer to the mean (SD) or median (min/max range) if not indicated otherwise

^FVC, FEV1 and/or DLCO <80% of predicted, and/or FEV1/FVC <0.7

Anti-RNP, anti-ribonucleoprotein; BMI, body mass index; PFT, pulmonary function test; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 sec; DLCO, diffusion capacity of carbon monoxide; VA, alveolar volume; TLC, total lung capacity; 6MWT, 6 min walk test; ESR, erythrocyte sedimentation rate; CRP, c-reactive protein; PGA, physician global assessment of disease activity; VAS, visual analogue scale

Table 5. Progression of HRCT findings (n = 37) and changes in pulmonary function tests (n = 38) in patients with juvenile MCTD

	Time 1	Time 2	*p* value
Disease duration at time of HRCT	8.8 (0.6-33.6)	17.8 (3.1-40.2)	NA
Disease duration at time of PFT	11.6 (3.3-30.9)	17.7 (2.3-41.2)	NA
Age at PFT examination	21.9 (6.5)	32.2 (6.7)	NA
Age at HRCT	21.7 (7.3)	29.3 (8.6)	NA
Time between HRCT scans		8.3 (2.7)	NA
Time between PFT		10.3 (1.0)	NA
FVC %	92.7 (11.4)	85.6 (15.6)	0.004
FEV1 %	94.6 (12.0)	85.9 (10.3)	0.001
FEV1/FVC ratio	0.87 (0.05)	0.84 (0.05)	NS
DLCO %	72.2 (14.0)	70.5 (11.3)	NS
DLCO/VA %	88.2 (15.7)	88.2 (15.1)	NS
ILD present, n (%)	9 (24)	10 (27)	NS
Ground glass attenuation, n (%)	3 (8)	0	NS
Reticular pattern, n (%)	7 (19)	10 (27)	NS
Reticular pattern grade 1, n (%)	8 (22)	9 (24)	NS
Reticular pattern grade 2, n (%)	4 (11)	6 (16)	NS
Reticular pattern grade 3, n (%)	0	1 (3)	NS
Percentage of lung parenchyma with ILD	2.0 (1-18)	4.0 (1-18)	NS

Numbers are in mean (SD) or median (min/max range) unless stated otherwise
HRCT, high resolution computed tomography; PFT, pulmonary function tests; ILD, interstitial lung disease; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; DLCO, diffusion capacity of carbon monoxide; VA, alveolar volume