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Anti-Ro52 autoantibodies are associated with interstitial lung disease and more severe disease in patients with juvenile myositis

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Abstract

Objectives: Anti-Ro52 autoantibodies are associated with more severe interstitial lung disease (ILD) in adult myositis patients with anti-aminoacyl tRNA synthetase autoantibodies. However, few studies have examined anti-Ro52 autoantibodies in juvenile myositis. The purpose of this study was to define the prevalence and clinical features associated with anti-Ro52 autoantibodies in a large cohort of patients with juvenile myositis.

Methods: We screened sera from 302 patients with juvenile dermatomyositis (JDM), 25 patients with juvenile polymyositis (JPM), and 44 patients with juvenile connective tissue disease-myositis overlap (JCTM) for anti-Ro52 autoantibodies by ELISA. Clinical characteristics were compared between myositis patients with and without anti-Ro52 autoantibodies.

Results: Anti-Ro52 autoantibodies were found in 14% of JDM, 12% of JPM, and 18% of JCTM patients. Anti-Ro52 autoantibodies were more frequent in patients with anti-aminoacyl tRNA synthetase (64%, $p<0.001$) and anti-MDA5 (31%, $p<0.05$) autoantibodies. After controlling for the presence of myositis-specific autoantibodies, anti-Ro52 autoantibodies were associated with the presence of ILD (36% vs 4%, $p<0.001$). Disease course was more frequently chronic, remission was less common, and an increased number of medications was received in anti-Ro52 positive patients.

Conclusions: Anti-Ro52 autoantibodies are present in 14% of juvenile myositis patients and are strongly associated with anti-MDA5 and anti-aminoacyl tRNA synthetase autoantibodies. In all juvenile myositis patients, those with anti-Ro52 autoantibodies were more likely to have ILD. Furthermore, patients with anti-Ro52 autoantibodies have more severe disease and a poorer prognosis.

Keywords

myositis; juvenile idiopathic inflammatory myopathies; anti-Ro52 autoantibodies; myositis associated autoantibodies; interstitial lung disease

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INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of systemic autoimmune diseases characterized by weakness, chronic inflammation of skeletal muscles, and elevated serum muscle enzyme levels.[1] Many patients also have extramuscular manifestations, including involvement of the skin, lungs, and/or joints. Most IIM patients have a myositis-specific autoantibody (MSA), defined as an autoantibody found only in IIM patients, which are typically mutually exclusive.[2] In contrast, myositis-associated autoantibodies (MAAs) are found in IIM, but may also be present in patients with other autoimmune diseases and may be seen in association with an MSA or other MAAs.

MSAs are associated with specific phenotypes.[23] For instance, anti-melanoma differentiation-associated gene 5 (MDA5) autoantibodies are associated with cutaneous ulceration and palmar papules, minimal muscle involvement, arthritis, interstitial lung disease (ILD), and a high fatality rate.[4–7] In contrast, patients with autoantibodies recognizing histidyl-tRNA synthetase (i.e., Jo1), have anti-synthetase syndrome, a unique multisystem autoimmune disease characterized by a combination of myositis, ILD, arthritis, Raynaud's phenomenon, fever, and/or mechanic's hands.[8] Of note, while many phenotypic features are similar between juvenile and adult IIM with the same MSAs, there are some important differences. For example, adults with anti-p155/140 (TIF-1) autoantibodies have an increased risk of malignancy, whereas anti-p155/140 (TIF-1) autoantibody positive children do not.[29]

In adult IIM patients, the most common MAA is anti-Ro52.[10] Interestingly, anti-Ro52 autoantibodies often co-occur with anti-Jo1 autoantibodies[11] and adult patients with both autoantibodies have more severe ILD and more frequently develop lung fibrosis than those with anti-Jo1 autoantibodies alone.[1213] In addition, higher anti-Ro52 autoantibody titers are associated with the development of more severe ILD[14], myositis, and joint impairment in anti-Jo1-positive adult patients.[15] Patients with both anti-Jo1 and anti-Ro52 autoantibodies have a poorer response to various immunosuppressive drugs and a decrease in survival.[1315]

A recent analysis of 22 children with myositis revealed that 23% had anti-Ro52 autoantibodies, although specific clinical associations were not examined.[16] The purpose of this study was to define the prevalence of and clinical features associated with anti-Ro52 autoantibodies in a large cohort of patients with juvenile myositis.

PATIENTS AND METHODS

Patients and serum samples

Of the 543 patients from the Childhood Myositis Heterogeneity Collaborative Study who were enrolled between 1989 and 2016 with probable or definite myositis by Bohan and Peter criteria,[17] those with a serum sample available for autoantibody testing at the time of enrollment were included in the study. Among the 317 juvenile myositis patients included, 302 (81.4%) had juvenile dermatomyositis (JDM), 25 (6.7%) had juvenile polymyositis (JPM) and 44 (11.9%) had juvenile connective tissue disease–myositis (JCTM) overlap. The JCTM subgroup included patients meeting criteria for myositis and another autoimmune

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disease, including 13 with juvenile systemic lupus erythematosus, 11 with juvenile systemic sclerosis, 7 patients with juvenile idiopathic arthritis, and 13 with other autoimmune conditions including autoimmune hepatitis, eosinophilic fasciitis, diabetes mellitus, lichen sclerosis, linear morphea, psoriasis, Sjögren's syndrome, and ulcerative colitis. Sera from 90 healthy control children enrolled in the same studies were available.

All subjects were enrolled in institutional review board-approved natural history studies as previously described,[18] and all provided informed consent. A standardized physician questionnaire captured demographics, clinical and laboratory features, environmental exposures at illness onset or diagnosis, as well as therapeutic usage and responses.[18] Seven organ system symptom scores at diagnosis, defined as the number of symptoms present divided by the number of symptoms assessed, and an overall clinical symptom score as the average of the seven individual organ symptom scores, were calculated as previously described.[19–21] In 7 of 33 patients, the presence of ILD was diagnosed by high resolution computed tomography (HRCT) and lung biopsy. In 11 of 33 patients, ILD was diagnosed by HRCT alone and in 5 patients, ILD was diagnosed by biopsy alone. Seven patients were diagnosed with ILD by chest radiographic imaging combined with pulmonary function testing and did not undergo HRCT or lung biopsy. Three patients did not have imaging records available and the diagnosis of ILD was based on physician documentation in the medical record. Complete clinical response and remission were defined as at least 6-months of inactive disease on or off therapy, respectively.[20] A course of treatment was defined as a single episode from beginning of administration of a given medication to the termination of treatment with that medication, or combination of medications, in each patient. Medical record review, conducted in >75% of patients, verified the clinical, demographic, laboratory and therapeutic data contained in the physician questionnaires. Follow up visits occurred in 55% of patients, with an average time from enrollment date to final evaluation of 4.3 years. Patient characteristics in our cohort are comparable with other registry-based JDM cohorts in terms of demographics and disease manifestations.[22–25]

Autoantibody assays

Anti-Ro52 autoantibodies were detected using an enhanced performance Ro52 enzyme-linked immunosorbent assay (ELISA) [SS-A 52 ELISA, Quanta Lite, INOVA Diagnostics, San Diego, CA] according to the manufacturer's instructions. Other myositis autoantibodies were detected as previously described.[1826]

Analysis

Dichotomous variables were expressed as percentages and absolute frequencies, and continuous features were reported as means and SD. Pairwise comparisons for categorical variables between groups were made using χ^2 test or Fisher's exact test, as appropriate, while continuous variables were compared using Student's t-test. Logistic and linear regression were used to adjust the comparisons for possible confounding variables, including the year of diagnosis, length of follow-up and MSAs. Creatine kinase, a highly positively skewed variable, was expressed as median, first and third quartile for descriptive purposes and transformed through a base-10 logarithm for analysis. All statistical analyses were

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performed using Stata/MP V.14.1 (StataCorp LLC, College Station, Texas). As this was an exploratory study, a two-sided P value of ≤0.05 was considered statistically significant.

RESULTS

Prevalence and demographics of patients with anti-Ro52 autoantibodies

Anti-Ro52 autoantibodies were more prevalent in patients with juvenile IIM (JIIM) than in healthy control children (14% vs 1%). Sera from 14% of patients with JDM, 12% with JPM, and 18% with JCTM had anti-Ro52 autoantibodies (Figure 1, Table 1). There were no significant differences in gender, race, age at diagnosis, or delay to diagnosis between juvenile myositis patients with and without anti-Ro52 autoantibodies (Table 2).

Prevalence of anti-Ro52 autoantibodies among myositis-specific autoantibody subgroups

Of those patients positive for anti-Ro52 autoantibodies, 26% had co-existing anti-p155/140 (TIF-1) autoantibodies, 21% had anti-NXP-2 autoantibodies, 19% had anti-MDA5 autoantibodies, 18% had anti-aminoacyl tRNA synthetase autoantibodies, 4% had anti-Mi2 autoantibodies, 4% had anti-HMGCR autoantibodies, and 9% were MSA negative (Table 2). Anti Ro-52 autoantibodies were significantly increased in the anti-MDA5 and anti-aminoacyl tRNA synthetase autoantibody subgroups than in other MSA subgroups (Table 1). For instance, anti-Ro52 autoantibodies co-existed in 31% of juvenile IIM sera with anti-MDA5 autoantibodies and 64% of those with anti-aminoacyl tRNA synthetase autoantibodies (Table 1). Similarly, anti-MDA5 autoantibodies co-existed in 19% of anti-Ro52 autoantibody positive sera and 7% of anti-Ro52 autoantibody negative sera. Anti-aminoacyl tRNA synthetase autoantibodies co-existed in 18% of anti-Ro52 autoantibody positive sera and 2% of anti-Ro52 autoantibody negative sera (Table 2). Less than 15% of those with anti-p155/140 (TIF1), anti-nuclear matrix protein-2 (NXP2), anti-signal recognition particle (SRP), or anti-Mi2 autoantibodies, and only 5% of those without an MSA were anti-Ro52 positive (Table 1).

Pulmonary manifestations among patients with anti-Ro52 autoantibodies

After controlling for the presence of MSAs (including anti-aminoacyl tRNA synthetase and anti-MDA5 autoantibodies) a multivariate analysis showed anti-Ro52 autoantibodies were highly associated with pulmonary involvement. Overall, patients with anti-Ro52 autoantibodies more often had ILD (36% vs 4%), dyspnea on exertion (59% vs 25%), and a higher early pulmonary score (mean 0.18 vs 0.08) than those without these autoantibodies (Table 3). Within the anti-MDA5 autoantibody positive subgroup, Ro52 reactivity was even more strongly associated with ILD: 70% of those with co-existing anti-Ro52 autoantibodies had ILD compared to only 9% of those who were anti-Ro52 negative (Table 4). Similarly, among the anti-aminoacyl tRNA synthetase autoantibody subgroup, 100% of anti-Ro52 autoantibody positive and 40% of anti-Ro52 negative patients had ILD (Table 4). Other pulmonary manifestations were also associated with Ro52 reactivity within the anti-MDA5 and anti-aminoacyl tRNA synthetase autoantibody subgroups. Specifically, among those patients with anti-MDA5 autoantibodies, patients who also were positive for anti-Ro52 autoantibodies more often had dyspnea on exertion (90% vs 27%) and higher early pulmonary scores than those who were anti-Ro52 autoantibody negative. Only 1 of 33

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patients with ILD in our JIIM cohort had rapidly progressive ILD, and this patient was positive for both anti-MDA5 and anti-Ro52 autoantibodies. In patients with anti-aminoacyl tRNA synthetase autoantibodies, anti-Ro52 autoantibody positive patients had increased frequency of dyspnea on exertion (89% vs 40%), although this did not reach statistical significance. Patients with co-existing anti-p155/140 (TIF-1) and anti-Ro52 autoantibodies also had an increased frequency of ILD (15% vs 1%) and dyspnea on exertion (50% vs 16%) compared to anti-p155/140 (TIF-1) autoantibody positive patients who were anti-Ro52 autoantibody negative (Table 4). Of note, in the MSA negative subgroup, none of 5 anti-Ro52 autoantibody positive patients had ILD (Table 4). The association of anti-Ro52 autoantibodies with ILD was significant within the JDM clinical subgroup: 33% of JDM patients with anti-Ro52 autoantibodies had ILD compared to 1% of anti-Ro52 negative JDM patients (Table 4).

Other clinical manifestations among patients with anti-Ro52 autoantibodies

Independent of MSA status, anti-Ro52 autoantibodies were also associated with Raynaud's phenomenon (23% vs 14%) (Table 3). Furthermore, within the anti-NXP2 subgroup, Ro52 reactivity was associated with more cutaneous involvement: patients with both anti-NXP2 and anti-Ro52 autoantibodies had a higher prevalence of V- or Shawl-sign rashes (55% vs 17%) and linear extensor erythema (64% vs 20%) than anti-NXP2 autoantibody positive patients without anti-Ro52 autoantibodies. Those with both anti-NXP2 and anti-Ro52 autoantibodies also had more frequent gastroesophageal regurgitation (55% vs 17%). Within the anti-MDA5 subgroup, however, anti-Ro52 autoantibodies were associated with less frequent linear extensor erythema (11% vs 50%). Patients with anti-Ro52 autoantibodies also had a higher mean early cardiac score, defined by the presence of cardiac symptoms at diagnosis.[19] There were no other significant differences in the prevalence of the muscle, lung, joint, cutaneous, gastrointestinal, or constitutional manifestations between patients with and without anti-Ro52 autoantibodies in univariate or multivariate analysis, or in examining these features in anti-Ro52 autoantibody positive patients in the presence of another MSA.

Disease severity among patients with anti-Ro52 autoantibodies

Several other differences in outcomes and medications received between patients positive and negative for anti-Ro52 autoantibodies suggested that anti-Ro52 autoantibodies are associated with more severe disease (Table 5). The disease course in patients with anti-Ro52 autoantibodies was more often chronic continuous (78% vs 52%) and less often monocyclic (3% vs 25%). Anti-Ro52 positive patients were more often American College of Rheumatology (ACR) functional class 4 (11% vs 4%) at the last clinical evaluation and had a higher mean ACR functional class score at that assessment. Anti-Ro52 autoantibodies were also associated with an increased total number of medications received (mean 4.8 vs 3.8). Anti-Ro52 autoantibody positive patients more often received intravenous pulse steroids (79% vs 52%). Anti-Ro52 autoantibody positive patients less often achieved clinical remission (5% vs 27%). Lastly, on univariate analysis, but not multivariable analysis, patients with anti-Ro52 autoantibodies less often experienced a complete clinical response (17% vs 32%) and had more medication treatment trials per year (mean 3.5 vs 2.2).

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Those with both anti-NXP2 and anti-Ro52 autoantibodies also more often had a severe (class IV) ACR functional class (27% vs 3%) and more frequent wheelchair use (60% vs 20%) as compared to patients positive for anti-NXP2 who were anti-Ro52 autoantibody negative. There was no other association of co-existing MSAs and anti-Ro52 autoantibodies on clinical outcomes or medications received.

Anti-Ro52 autoantibody titers

Anti-Ro52 autoantibody titers did not significantly differ between JDM, JPM, and JCTM groups. Overall, we found that higher anti-Ro52 titers are associated with shorter follow-up time, more treatment trials per year, higher early total symptom score, more total number of medications used, higher total functional class, higher severity at onset, higher early pulmonary score, higher early constitutional symptoms score, and higher total functional class in patients with juvenile IIM (all $p<0.05$; data not shown). However, as the Spearman correlation coefficients were ≤ 0.2 for each association, the clinical significance of high autoantibody titers is modest.

DISCUSSION

Here, we utilized a large cohort of juvenile myositis patients to study the prevalence and clinical significance of anti-Ro52 autoantibodies in children with IIM. We found anti-Ro52 autoantibodies to be strongly associated with ILD and other pulmonary manifestations in juvenile myositis patients. We also found that children with anti-Ro52 autoantibodies have more severe disease, underwent more intense treatment regimens, and had lower rates of disease remission than those without anti-Ro52 autoantibodies. In children with myositis, anti-Ro52 autoantibodies were associated with anti-aminoacyl tRNA synthetase autoantibodies, as previously described in adults.[11] We also found that anti-Ro52 autoantibodies were associated with anti-MDA5 autoantibodies in pediatric myositis patients, which has not been reported previously.

Importantly, our analyses indicate that the presence of anti-Ro52 autoantibodies is strongly associated with ILD, even after adjusting for the presence of MSAs such as anti-MDA5 and anti-aminoacyl tRNA synthetase autoantibodies. Indeed, the association of Ro52 reactivity with ILD is not limited to the anti-MDA5 and anti-aminoacyl tRNA synthetase autoantibody subgroups, but extends to other MSA subgroups that are not classically associated with ILD, such as children with anti-p155/140 (TIF-1) autoantibodies. However, none of the 5 anti-Ro52 autoantibody positive MSA-negative patients had ILD. Current practice encourages screening juvenile myositis patients for MSAs such as anti-MDA5 and anti-aminoacyl tRNA synthetase autoantibodies, as these autoantibodies confer risk for developing ILD and their presence is a determinant of clinical management and patient prognosis. In light of the current findings demonstrating that anti-Ro52 autoantibodies are an independent predictor of ILD, screening juvenile myositis patients for these autoantibodies may also be prudent.

In adult patients with IIM, anti-Ro52 autoantibodies have been associated with poorer response to immunosuppressive drugs and decreased survival.[13,15] Similarly, in our juvenile cohort, anti-Ro52 autoantibodies are associated with more severe disease and poorer outcomes. Of note, the presence of anti-Ro52 autoantibodies was associated with a higher

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early cardiac score which is a measure of patient reported cardiac symptoms including palpitations, chest pain, and syncope. However, among the 9 anti-Ro52-positive patients with one or more of these symptoms, only 3 had EKG changes or ECHO abnormalities. As the severity of other clinical manifestations, including muscle, joint, skin, gastrointestinal, and systemic features were not associated with Ro52 reactivity, it seems likely that disease severity seen in the anti-Ro52 positive patients is a consequence of pulmonary disease. Additional studies are required to clarify this point. Nonetheless, our findings highlight the potential utility of anti-Ro52 autoantibodies as a predictor of disease severity and poor prognosis in juvenile myositis, which underscores the potential utility of screening juvenile IIM patients for anti-Ro52 autoantibodies.

Of particular significance is the novel association of anti-Ro52 autoantibodies and anti-MDA5 autoantibodies in our JIIM cohort. In adult IIM patients, anti-Ro52 autoantibodies often co-occur with anti-Jo1 autoantibodies, and in adult anti-Jo1 positive patients, Ro52 reactivity is associated with more severe ILD. A small case series reported co-existing anti-Ro52 autoantibodies in 6 of 13 anti-MDA5 autoantibody positive patients, 5 of whom had rapidly progressive ILD.[27] Interestingly, only 1 of 33 patients with ILD in our JIIM cohort had rapidly progressive ILD and this patient was positive for both anti-MDA5 and anti-Ro52 autoantibodies.

Although we have now established an association between anti-aminoacyl tRNA synthetase and anti-Ro52 autoantibodies not only in adults, but also in children, it remains unclear why these autoantibodies co-occur. It has been proposed that local autoantibody production induced by type I IFN[28] could be a driving force behind the production of both anti-Jo1 and anti-Ro52 autoantibodies, given the increase in B-cell activating factor (BAFF) receptors in the sera of IIM patients with these autoantibodies.[29] In the current study of juvenile IIM, we now also demonstrate an association between anti-MDA5 and anti-Ro52 autoantibodies. Interestingly, both MDA5 and Ro52 are cytosolic, interferon (IFN)-induced proteins; perhaps concurrent over-expression of these proteins in juvenile IIM patients leads to the development of autoimmunity against both. However, we do not have adequate type I IFN measurements to further examine this hypothesis.

This current study has several limitations. First, this cohort of patients with juvenile myositis had some data collected retrospectively, resulting in some missing data, and was collected over more than 20-years, with potential chronology bias. However, we adjusted the variables of this study for the year of diagnosis and tested the distribution of missing values across groups and did not find evidence of a significant bias. Second, although imaging studies were available to confirm the diagnosis of ILD in more than 90% of patients who had ILD, pulmonary function testing data were not available for many of the patients, as a number of the children were of young age when such testing is unreliable in children. Thus, we were not able to study whether ILD patients with anti-Ro52 autoantibodies had more severe pulmonary dysfunction than those without these autoantibodies. Also, we cannot confirm the absence of ILD as many of the children without clinical suspicion of ILD did not have imaging and/or pulmonary function testing. This however, is a limitation of standard clinical care in pediatric patients who have challenges to undergo such testing.

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Overall, this study shows that anti-Ro52 autoantibodies are present in 14% of patients with juvenile myositis and are strongly associated with ILD, more severe illness, and poorer outcomes, even when correcting for the co-existence of MSAs. In juvenile myositis patients, anti-Ro52 autoantibodies are associated not only with the presence of anti-synthetase autoantibodies, as previously reported in adult myositis patients, but also with anti-MDA5 autoantibodies, and the co-existence of these MSAs increases the likelihood of ILD and poor outcome. The current standard of care in patients with juvenile myositis who have reactivity to MSAs associated with pulmonary manifestations (such as anti-MDA5 and anti-aminoacyl tRNA synthetase autoantibodies) is to have a high index of suspicion for the development of ILD and modify management accordingly. Our data suggest that testing for anti-Ro52 autoantibodies may also have a role in disease monitoring, management, and patient prognosis in juvenile myositis patients.

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KEY MESSAGES

What is already known about this subject?

- The clinical features and prognosis of juvenile myositis patients with anti-Ro52 autoantibodies was poorly defined.

What does this study add?

- Approximately 15% of a large North American cohort of juvenile myositis patients have anti-Ro52 autoantibodies.
- Juvenile myositis patients with anti-Ro52 autoantibodies are more likely to develop interstitial lung disease.
- Anti-Ro52 autoantibodies are more common in juvenile myositis patients with anti-MDA5 and anti-synthetase autoantibodies.
- Juvenile myositis patients with anti-Ro52 autoantibodies more often have a chronic disease course and require more medications.

How might this impact on clinical practice?

Anti-Ro52 autoantibodies are useful prognostic markers for ILD and severe disease in juvenile myositis patients.

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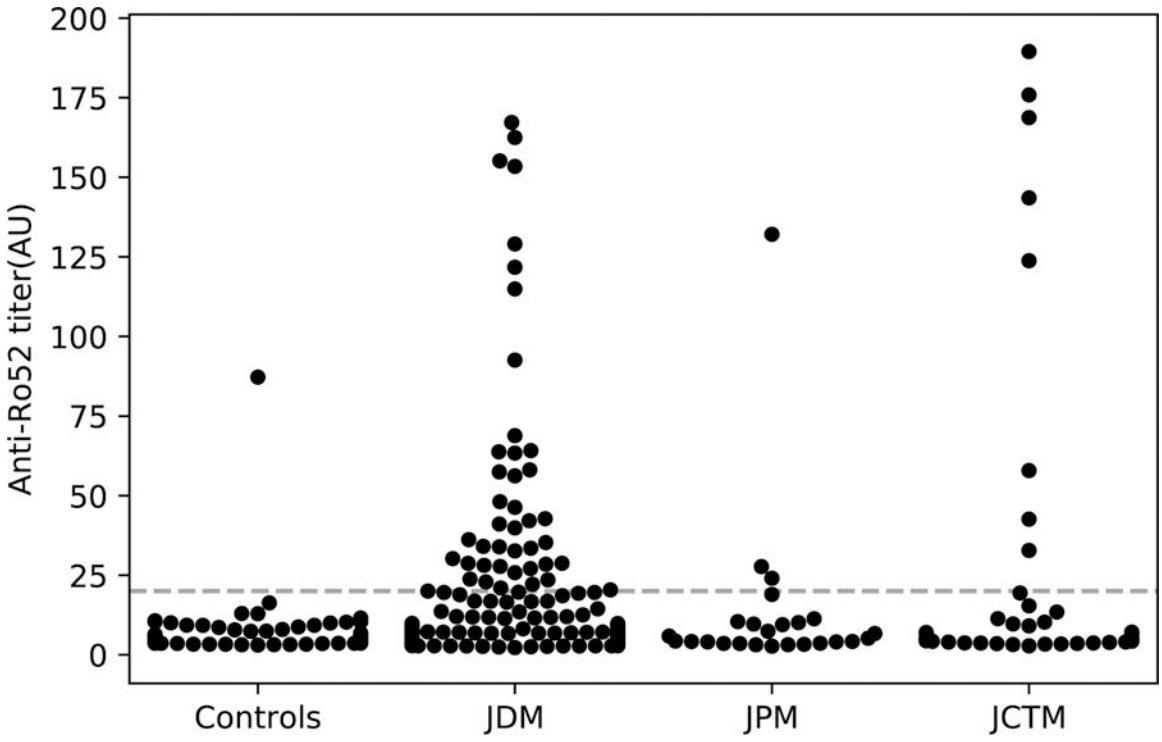

Figure 1. Swarm plot of anti-Ro52 autoantibody ELISA results for juvenile healthy controls and JIIM patients divided into JDM, JPM, and JCTM.

The dashed line of 20 units indicates the cut-off value for anti-Ro52 autoantibody positivity. Out of 371 JIIM patients, 53 (14%) were positive for anti-Ro52 autoantibodies by ELISA. Of these patients, 42 had JDM, 3 had JPM, and 8 had JCTM. Out of 90 juvenile healthy controls, one patient (1.1%) was positive for anti-Ro52 autoantibodies by ELISA.

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Table 1.

Prevalence of anti-Ro52 autoantibodies among patients with juvenile myositis.

Clinical subgroup	Anti-Ro52 autoantibody positive % (n/N)
Juvenile myositis (N=371)	14% (n=53) ***
Juvenile dermatomyositis (N=302)	14% (n=42) ***
Juvenile polymyositis (N=25)	12% (n=3) *
Juvenile connective tissue-disease myositis (N=44):	18% (n=8) ***
Juvenile lupus erythematosus (N=13)	23% (n=3) **
Juvenile systemic sclerosis (N=11)	0% (n=0)
Juvenile idiopathic arthritis (N=7)	29% (n=2) *
Other autoimmune diseases[a] (N=13)	23% (n=3) **
Myositis specific autoantibody subgroup	
Anti-p155/140 (TIF-1) (N=119)	11% (n=13)
Anti-NXP2 (N=77)	14% (n=11)
Anti-MDA5 (N=32)	31% (n=10) *
Anti-aminoacyl tRNA synthetase (N=14)	64% (n=9) ***
Anti-SRP (N=7)	0% (n=0)
Anti-Mi2 (N=13)	15% (n=2)
Anti-HMGCR (N=4)	50% (n=2)
MSA negative (N=96)	5% (n=5) **
Juvenile healthy controls (N=90)	1% (n=1)

* $p<0.05$

** $p<0.01$

*** $p<0.001$

Chi-squared or Fisheŕs exact tests were used to compare the percentage of positive patients compared with the percentage of negative patients within each myositis clinical and autoantibody subgroup.

Abbreviations: TIF-1: transcription intermediary factor 1, NXP2: nuclear matrix protein-2, MDA5: melanoma differentiation associated protein-5, SRP: signal recognition particle, HMGCR: 3-Hydroxy-3-Methylglutaryl-CoA Reductase, MSA: myositis specific autoantibody

[a] autoimmune hepatitis, eosinophilic fasciitis, fasciitis, juvenile diabetes mellitus, lichen sclerosis, linear morphea, psoriasis, Sjögren's syndrome, ulcerative colitis.

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Table 2.

General features of juvenile myositis patients with and without anti-Ro52 autoantibodies.

	Total (N=371) % (n/N) or Mean (SD)	Anti-Ro52 autoantibody positive (N=53) % (n/N) or Mean (SD)	Anti-Ro52 autoantibody negative (N=318) % (n/N) or Mean (SD)	p-value
Age at diagnosis	9.0 (4.4)	9.5 (4.7)	8.9 (4.3)	0.3
Age at enrollment	12.5 (7.1)	12.6 (7.7)	12.5 (7.0)	1.0
Delay to diagnosis (years)	0.7 (1.2)	0.55 (0.56)	0.75 (1.27)	0.3
Follow-up (years)	5.8 (6.4)	4.3 (6.4)	6.0 (6.4)	0.09
Female	71% (263/371)	74% (39/53)	70% (224/318)	0.6
Race				
White	65% (240/371)	57% (30/53)	66% (210/318)	0.2
Black	16% (59/371)	21% (11/53)	15% (48/318)	0.3
Hispanic	6% (24/371)	6% (3/53)	7% (21/318)	1.0
Other races [a]	13% (48/371)	17% (9/53)	12% (39/318)	0.3
Myositis-specific autoantibodies				
Anti-p155/140 (TIF-1)	33% (119/359)	26% (13/50) [b]	34% (106/309) [c]	0.2
Anti-NXP2	21% (77/366)	21% (11/52) [b]	21% (66/314) [c]	1.0
Anti-MDA5	9% (32/368)	19% (10/53)	7% (22/315) [c]	0.01
Anti-aminoacyl tRNA synthetase	4% (14/360)	18% (9/49) [b]	2% (5/311) [c]	< 0.001
Anti-SRP	2% (7/360)	0% (0/49) [b]	2% (7/311) [c]	0.6
Anti-Mi2	4% (13/354)	4% (2/49) [b]	4% (11/305) [c]	0.7
Anti-HMGCR	1% (4/371)	4% (2/53)	1% (2/318)	0.10
MSA negative	27% (96/362)	9% (5/53)	29% (91/309) [c]	0.002

Dichotomous variables were represented as percentage (count/total) and continuous variables as mean (SD). Chi-squared or Fisheŕs exact tests were used to compare dichotomous variables, as appropriate, while continuous variables were compared using Student́s t-test.

Abbreviations: TIF-1: transcription intermediary factor 1, NXP2: nuclear matrix protein-2, MDA5: melanoma differentiation associated protein-5, SRP: signal recognition particle, HMGCR: 3-Hydroxy-3-Methylglutaryl-CoA Reductase, MSA: myositis specific autoantibody.

[a] Asian (Korean, Japanese, Chinese, Indian, Filipino), Pacific Islands, American Indian.

[b] $N \neq 53$ due to missing data.

[c] $N \neq 318$ due to missing data.

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Table 3.

Clinical features of juvenile myositis patients with and without anti-Ro52 autoantibodies.

Signs/symptoms ever present	Total (N=371) % (n/N) or Mean (SD)	Anti-Ro52 autoantibody positive (N=53) % (n/N) or Mean (SD)	Anti-Ro52 autoantibody negative (N=318) % (n/N) or Mean (SD)	Univariate p-value	Multivariate p-value
Muscle involvement					
Proximal weakness	99% (369/371)	98% (52/53)	100% (317/318)	0.3	0.3
Myalgia	64% (234/363)	62% (32/52) [a]	65% (202/311) [b]	0.6	0.1
Distal weakness	47% (170/363)	46% (24/52) [a]	47% (146/311) [b]	0.9	0.9
Muscle atrophy	37% (136/367)	44% (23/52) [a]	36% (113/315) [b]	0.2	0.3
Falling episodes	45% (164/367)	44% (23/52) [a]	45% (141/315) [b]	0.9	1.0
Lung involvement					
Dyspnea on exertion	30% (109/366)	59% (30/51) [a]	25% (79/315) [b]	< 0.001	< 0.001
Interstitial lung disease	9% (33/369)	36% (19/53)	4% (14/316) [b]	< 0.001	< 0.001
Dysphonia	32% (118/367)	32% (17/53)	32% (101/314) [b]	1.0	0.7
Joint involvement					
Arthralgia	64% (236/369)	70% (37/53)	63% (199/316) [b]	0.3	0.4
Joint contractures	61% (224/370)	63% (33/52) [a]	60% (191/318)	0.6	0.7
Arthritis	51% (189/370)	60% (31/52) [a]	50% (158/318)	0.2	0.7
Skin involvement					
Heliotrope	79% (293/369)	87% (46/53)	78% (247/316) [b]	0.2	0.2
Gottrońs papules	82% (305/370)	77% (41/53)	83% (264/317) [b]	0.3	0.3
Malar rash	70% (259/371)	68% (36/53)	70% (223/318)	0.7	0.6
Photosensitivity	48% (172/362)	49% (25/51) [a]	47% (147/311) [b]	0.8	0.9
V or Shawl sign rash	31% (113/369)	42% (22/53)	29% (91/316) [b]	0.06	0.07
Linear extensor erythema	36% (130/363)	31% (16/52) [a]	37% (114/311) [b]	0.4	0.3
Calcinosis	29% (109/371)	28% (15/53)	30% (94/318)	0.9	0.1
Raynaudś phenomenon	15% (55/369)	23% (12/53)	14% (43/316) [b]	0.09	0.04
Mechanićs hands	7% (27/366)	9% (5/53)	7% (22/313) [b]	0.6	0.5
Gastrointestinal involvement					
Dysphagia	41% (151/370)	38% (20/53)	41% (131/317) [b]	0.6	1.0
Regurgitation	21% (77/370)	26% (14/53)	20% (63/317) [b]	0.3	0.5
Systemic involvement					
Weight loss	42% (155/369)	52% (27/52) [a]	40% (128/317) [b]	0.1	0.8

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Signs/symptoms ever present	Total (N=371) % (n/N) or Mean (SD)	Anti-Ro52 autoantibody positive (N=53) % (n/N) or Mean (SD)	Anti-Ro52 autoantibody negative (N=318) % (n/N) or Mean (SD)	Univariate p-value	Multivariate p-value
Fever	31% (112/358)	41% (21/51) [a]	30% (91/307) [b]	0.10	0.8
Muscle Enzymes					
Peak creatine kinase, IU/L	781 (252–5142)	1121 (225–3971)	750 (256–5249)	0.7	0.9
Peak aldolase, IU/L	20.0 (34.5)	18.0 (22.5)	20.3 (36.1)	0.6	0.3
Severity at onset	2.2 (1.1)	2.2 (1.7)	2.2 (0.9)	0.9	0.4
Early total symptom score	0.2 (0.1)	0.27 (0.14)	0.23 (0.11)	0.03	0.8
Early muscle score	0.4 (0.2)	0.37 (0.18)	0.38 (0.20)	0.7	0.5
Early joint score	0.5 (0.4)	0.48 (0.38)	0.45 (0.43)	0.6	0.1
Early cutaneous score	0.3 (0.1)	0.26 (0.15)	0.25 (0.14)	0.6	0.4
Early gastrointestinal score	0.1 (0.1)	0.08 (0.11)	0.07 (0.11)	0.6	1.0
Early pulmonary score	0.1 (0.2)	0.18 (0.23)	0.08 (0.14)	< 0.001	0.002
Early cardiac score	0.0 (0.1)	0.05 (0.12)	0.02 (0.07)	0.04	0.05
Early constitutional symptoms score	0.4 (0.3)	0.48 (0.34)	0.38 (0.26)	0.02	1.0

Dichotomous variables were represented as percentage (count/total), continuous variables as mean (SD) and the creatine kinase was presented as median (Q1-Q3). For the univariate analysis, dichotomous variables were compared using chi-squared or Fisheŕs exact tests, as appropriate while continuous variables were compared using Studentś t-test. Multivariate analysis used linear or logistic regression adjusted for length of follow-up, year of onset and autoantibodies. Creatine kinase was log-transformed prior to statistical analysis.

[a] $N \neq 53$ due to missing data.

[b] $N \neq 318$ due to missing data.

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Table 4:

Pulmonary features of juvenile myositis patients with and without anti-Ro52 autoantibodies within juvenile myositis clinical and autoantibody subgroups

	Anti-Ro52 autoantibody positive % (n/N) or Mean (SD)	Anti-Ro52 autoantibody negative % (n/N) or Mean (SD)	p-value
JDM subgroup (N=302)			
Interstitial lung disease	33% (14/42)	1% (3/258) [a]	< 0.001
Dyspnea on exertion	62% (26/42)	19% (50/258) [a]	< 0.001
Early pulmonary score	0.20 (0.22)	0.07 (0.13)	< 0.001
JPM subgroup (N=25)			
Interstitial lung disease	33% (1/3)	18% (4/22)	0.5
Dyspnea on exertion	50% (1/2) [a]	67% (14/21) [a]	1.0
Early pulmonary score	0.17 (0.29)	0.19 (0.20)	0.8
JCTM subgroup (N=44)			
Interstitial lung disease	50% (4/8)	19% (7/36)	0.09
Dyspnea on exertion	43% (3/7) [b]	42% (15/36)	1.0
Early pulmonary score	0.12 (0.25)	0.09 (0.16)	0.7
Anti-MDA5 autoantibody subgroup (N=32)			
Interstitial lung disease	70% (7/10)	9% (2/22)	0.001
Dyspnea on exertion	90% (9/10)	27% (6/22)	0.002
Early pulmonary score	0.29 (0.19)	0.02 (0.06)	< 0.001
Anti-aminoacyl tRNA synthetase autoantibody subgroup (N=14)			
Interstitial lung disease	100% (9/9)	40% (2/5)	0.03
Dyspnea on exertion	89% (8/9)	40% (2/5)	0.09
Early pulmonary score	0.31 (0.31)	0.27 (0.30)	0.8
Anti-p155/140 (TIF-1) autoantibody subgroup (N=119)			
Interstitial lung disease	15% (2/13)	1% (1/106)	0.03
Dyspnea on exertion	50% (6/12) [a]	16% (17/105) [a]	0.01
Early pulmonary score	0.16 (0.24)	0.06 (0.12)	0.01
Anti-NXP2 autoantibody subgroup (N=76)			
Interstitial lung disease	9% (1/11)	0% (0/65) [b]	0.1
Dyspnea on exertion	45% (5/11)	27% (18/66)	0.3

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	Anti-Ro52 autoantibody positive % (n/N) or Mean (SD)	Anti-Ro52 autoantibody negative % (n/N) or Mean (SD)	p-value
Early pulmonary score	0.16 (0.19)	0.10 (0.14)	0.2
MSA negative subgroup (N=96)			
Interstitial lung disease	0% (0/5)	10% (9/90)	1.0
Dyspnea on exertion	25% (1/4)	33% (30/90)	1.0
Early pulmonary score	0.04 (0.09)	0.08 (0.15)	0.5

Dichotomous variables were represented as percentage (count/total), continuous variables as mean (SD). For the univariate analysis, dichotomous variables were compared using chi-squared or Fisheŕs exact tests, as appropriate while continuous variables were compared using Student́s t-test.

Abbreviations: JDM: juvenile dermatomyositis, JPM: juvenile polymyositis, JCTM: juvenile connective tissue myositis; MDA5: melanoma differentiation associated protein-5, TIF-1: transcription intermediary factor 1, NXP2: nuclear matrix protein-2, SRP: signal recognition particle.

[a] Data missing for two patients within juvenile myositis clinical or autoantibody subgroup.

[b] Data missing for one patient within juvenile myositis clinical or autoantibody subgroup.

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Table 5.

Disease outcomes and medications used in juvenile myositis patients with and without anti-Ro52 autoantibodies

	Total (N=371) % (n/N) or Mean (SD)	Anti-Ro52 autoantibody positive (N=53) % (n/N) or Mean (SD)	Anti-Ro52 autoantibody negative (N=318) % (n/N) or Mean (SD)	Univariate p-value	Multivariate p-value
Disease					
Monocyclic course	22% (65/297)	3% (1/37) [b]	25% (64/260) [c]	0.003	0.02
Polycyclic course	23% (68/297)	19% (7/37) [b]	23% (61/260) [c]	0.5	0.9
Chronic continuous course	55% (164/297)	78% (29/37) [b]	52% (135/260) [c]	0.002	0.05
Steinbrocker functional class at final assessment					
Mean functional class	1.4 (0.8)	1.7 (1.0)	1.4 (0.8)	0.007	0.007
Functional class 1	70% (257/367)	53% (28/53)	73% (229/314) [c]	0.003	0.09
Functional class 2	21% (77/367)	34% (18/53)	19% (59/314) [c]	0.01	0.3
Functional class 3	4% (13/367)	2% (1/53)	4% (12/314) [c]	0.7	0.2
Functional class 4	5% (20/367)	11% (6/53)	4% (14/314) [c]	0.05	0.008
Mortality	4% (13/371)	6% (3/53)	3% (10/318)	0.4	0.4
Hospitalized	58% (206/355)	66% (35/53)	57% (171/302) [c]	0.2	0.4
Mean number of hospitalizations	1.3 (1.9)	1.3 (1.4)	1.3 (2.0)	0.9	0.8
Wheelchair use	19% (68/360)	24% (12/50) [b]	18% (56/310) [c]	0.3	0.2
Response to treatment					
Complete clinical response	30% (91/304)	17% (7/42)	32% (84/262) [c]	0.04	0.4
Remission	24% (74/312)	5% (2/43)	27% (72/269) [c]	0.002	0.05
Total number of medications used	3.9 (2.1)	4.8 (2.5)	3.8 (2.0)	0.003	0.05
Treatment trials per year	2.3 (2.8)	3.5 (3.0)	2.2 (2.7)	0.004	0.1
Medications received					
Oral steroids	99% (309/312)	100% (43/43) [b]	99% (266/269) [c]	1.0	.
Intravenous pulsed steroids	56% (174/312)	79% (34/43) [b]	52% (140/269) [c]	< 0.001	0.03
Methotrexate	74% (230/312)	86% (37/43) [b]	72% (193/269) [c]	0.05	0.4
Intravenous immunoglobulin	36% (112/312)	49% (21/43) [b]	34% (91/269) [c]	0.06	0.08
Other DMARDs	23% (73/312)	35% (15/43) [b]	22% (58/269) [c]	0.06	0.3

Dichotomous variables were represented as percentage (count/total), continuous variables as mean (SD). For the univariate analysis, dichotomous variables were compared using chi-squared or Fisheŕs exact tests, as appropriate while continuous variables were compared using Studentś t-test. Multivariate analysis used linear or logistic regression adjusted for length of follow-up, year of onset and autoantibodies.

Abbreviations: ACR: American College of Rheumatology, DMARDs: disease modifying anti-rheumatic agents

[a] Azathioprine, Chlorambucil, Chloroquine, Colchicine, Cyclophosphamide, Cyclosporine, Dapsone, Hydroxychloroquine, Intravenous Immunoglobulin, Lefluonmide, Methotrexate, Mycophenolate mofetil, Sodium thiosulfate, Quinacrine

[b] N ≠ 53 due to missing data

[c] N ≠ 318 due to missing data

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