Myositis-specific autoantibodies and their associated phenotypes in juvenile dermatomyositis: data from a German cohort

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Abstract

Objective

To describe a German cohort of patients with juvenile dermatomyositis (JDM) and to evaluate clinical manifestations, disease course and prognosis in JDM patients with a certain myositis-specific autoantibody.

Methods

Cross-sectional data on patients with JDM documented in the National Paediatric Rheumatologic Database in Germany between 2014 and 2016 were analysed. In a subgroup of the cohort, MSAs were determined with a commercial multiplex array, and a retrospective chart review was conducted to specify the clinical phenotype and patient outcome.

Results

The total cohort consisted of 196 patients with JDM (mean age 12.2±4.0 years, mean disease duration 5.1±3.8 years, 70% female). Apart from typical skin changes and muscle weakness, 41% of patients also had arthritis and/or contractures, 27% had calcinosis and approximately 10% had interstitial lung disease. Immunoblot testing was performed on the sera of 91 (46%) patients, detecting MSAs in 44% of patients. Patient groups with specific MSAs differed in clinical characteristics such as calcinosis, dysphagia, and lung and joint involvement. The extent of muscle weakness evaluated by the Childhood Myositis Assessment Scale was significantly associated with an increased level of creatine kinase. Patients with anti-MDA5 were particularly affected by polyarthritis of the small joints. After 5 years, 51patients of the MSA cohort (56.0%) achieved an inactive disease state, 12/51 (23.5%) were off therapy.

Conclusion

Patients with JDM in Germany show a broad spectrum of clinical manifestations that can be grouped into homogeneous groups using MSA, which also helps to predict the course and prognosis of the disease.

Key words

juvenile dermatomyositis, myositis-specific autoantibodies, outcome, clinical phenotype, arthritis

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Received on March 10, 2020; accepted in revised form on September 21, 2020.

Competing interests: K. Minden has received honoraria for lectures/scientific contributions from GSK, Sanofi, Abbvie, Pfizer and Medac.
F. Dressler has received honoraria for presentations and/or participation in advisory boards for Novartis, Pfizer and Abbvie.
P.T. Oommen has received research support from Novartis.
The other authors have declared no competing interests.

Introduction

Juvenile dermatomyositis (JDM) is the most common idiopathic inflammatory myopathy (IIM) in children and adolescents, with an incidence of two to four per million (1-4), varying in different ethnic groups. JDM is characterised by a weakness of the proximal muscles and pathognomonic skin manifestations, but other organ systems, such as the gastrointestinal, cardiovascular and respiratory system, or the joints can also be involved. Serious complications may occur, *e.g.* calcinosis, lipodystrophy or interstitial lung disease (ILD). Due to its heterogeneous presentation, the diagnosis of JDM can be challenging, although the understanding of the disease and diagnostic methods, *e.g.* the detection of autoantibodies, have improved over the last few years. Myositis- specific autoantibodies (MSAs) are almost exclusively found in idiopathic inflammatory myopathies (IIMs), while myositis-associated autoantibodies (MAAs) also occur in other autoimmune diseases such as overlap syndromes. Both antibody groups were first described in adult patients, and data from large cohorts about MSAs in JDM are limited to the US and UK thus far (5, 6).

In this study, we investigated the clinical characteristics, treatments and outcomes of a German JDM cohort derived from the National Paediatric Rheumatology Database (NPRD). Furthermore, we analysed the specific JDM phenotypes associated with MSAs and evaluated differences in disease outcome and response to treatment in the MSA subgroups.

Methods

Patients

Cross-sectional data of JDM patients enrolled in the NPRD at paediatric rheumatology centres across Germany between 2014 and 2016 were analysed. Physicians and patients (from the age of 8 years on) or parents documented demographic and clinical data annually on standardised, disease- specific questionnaires. By adding MRI as a muscular criterion for the diagnosis of JDM in our study, patients were diagnosed with JDM if they had typical skin lesions and at least two other criteria (including MRI) from Bohan and Peter, thus including both definite and probable cases. Patients aged 18 years or younger with a definitive or probable diagnosis of JDM and with documentation in the NPRD in at least one year between 2014 and 2016 were included. Attending physicians reported the clinical manifestations (typical skin lesions, arthritis/joint contractures, muscle weakness/pain, interstitial lung disease (ILD)), diagnostic methods applied (biopsy, magnetic resonance imaging (MRI), electromyography), laboratory results and current treatment. The Physician's Global Assessment of Disease Activity (PhGA) was reported on a numeric rating scale (NRS) from 0–10 (7). In addition, the JDM Disease Activity Score (DAS) (8) and the Manual Muscle Test (MMT) (7) were completed. Disease duration was defined as the time from symptom onset until time of assessment.Paediatric rheumatology centres participating in the NPRD were offered to send serum samples from JDM patients to Labor Berlin, the core facility for laboratory analysis of the Charité hospital, for central determination of MSAs and MAAs. Out of the 17 centres that provided data about JDM patients in the NPRD, 13 centres sent serum samples. For patients whose sera were examined for MSAs and MAAs, referred to as the MSA cohort, a retrospective chart review was performed including all available medical documents and comprised the evaluation of the disease course at three time points: the first 6 months of observation under paediatric care, referred to as disease onset; during the disease course; and at the last consultation. Skin symptoms such as facial and heliotropic erythema, Gottron papules, ulcers of skin or mucosa and calcinosis were documented. Pulmonary involvement was assumed in the case of pathologic pulmonary function and interstitial lung disease confirmed by corresponding changes in the computed tomography (CT).

Moreover, the distribution pattern of arthritis over the full course of disease was documented. In addition to the MMT documented in the NPRD, the values of the Childhood Myositis

Assessment Scale (CMAS) (9) reflecting muscle strength and endurance were recorded. The mean of the lowest ever-recorded scores for the CMAS and MMT per patient group with a specific MSA were used to compare the extent of muscle weakness during the disease course. Detailed information about previous and current therapies, including oral and intravenous glucocorticoids, conventional synthetic and biologic disease-modifying anti-rheumatic drugs (csDMARDS and bDMARDs, respectively) and intravenous immunoglobulins (IVIG), was recorded.

During the first 6 months of specialised care at a paediatric rheumatology centre, information on creatine kinase (CK) and aspartate-aminotransferase (AST) levels was collected and evaluated as normal, normal to twofold, twofold to threefold and more than threefold elevated according to the reference values of the corresponding laboratory. If more than one value was available in the first 6 months of observation, the highest value was taken into account.

At the last follow-up, the attending physician assessed the disease course so far (monocyclic = single phase of active disease and free of all clinical and biochemical signs of the disease on tapered/off medication, multi-cyclic = recurrence of active disease after a phase of remission while tapering or off medication; or chronic-progressive course = no tapering of medication possible or even escalation of therapy) and evaluated the disease activity on a numeric rating scale of 0–10. Since the variables best suited to classify the disease as inactive in a JDM patient according to PRINTO (at least 3 of 4 of the following criteria: creatine kinase ≤150, CMAS ≥48, MMT ≥78 and PhyGloVAS ≤0.2 [10]), were not available in combination at the last follow-up for many patients due to the retrospective study design, only the PhGA of disease activity was used: Patients with PhGA ≤1 were regarded as being in an inactive disease state and those with PhGA ≤1 and off medication were regarded as being in remission.

Mobility (wheelchair use, impaired or unimpaired walking ability, ability to attend school sport classes with or without limitations) was assessed at the last consultation. The study protocol was approved by the ethics committee of the Charité - Universitätsmedizin Berlin. All parents and patients from the age of 8 years on gave their informed assent/consent for participation. The National Paediatric Rheumatological Database has been funded by the German Children Arthritis Foundation (Deutsche Kinder-Rheumastiftung), AbbVie, Pfizer, Chugai, GSK and Novartis.

Detection of myositis-specific autoantibodies

All serum samples were analysed in the specialised laboratory centre Labor Berlin using the *in vitro* immunoassay "EUROLINE AutoImmune Inflammatory Myopathies" at the same time, thereby minimising methodological differences within our cohort. This line-blot consists of membrane strips that are coated with antigens to autoantibodies may attach and are made visible by a colour reaction forming a dark band. The assay includes a series of MSAs (anti-NXP-2, anti-TIF1γ, anti-MDA-5, anti-SRP, anti-Mi-2, anti-OJ, anti-EJ, anti-PL-7, anti-PL-12, anti-Jo-1, and anti-SAE) as well as MAAs (anti-Ku, anti-PM-75, anti-PM-100 and anti-Ro-52). It has been evaluated as suitable and reliable in the diagnostic workup for myositis (11, 12). Although the test kit offered a graduation depending on the level of MSA detected, the role of quantity was not further investigated, and all results greater or equal one plus (+, ++, +++) were recorded as positive.

Statistical analysis

SAS v. 9.4 (SAS Institute, Cary, North Carolina) was used for data management and statistical analysis. Absolute and relative frequencies are reported for categorical variables, and the mean, median, standard deviation and interquartile range are presented for continuously distributed data. Patients were grouped according to the presence of one MSA. Clinical characteristics of the MSA groups were compared by a χ^2 test for categorical variables and analysis of variance for continuously distributed variables. Spearman correlations were calculated for laboratory parameters (CK and AST), with the scores measuring muscle strength, such as MMT and CMAS. The joint involvement was assessed by counting the number of affected joints during the observation period. Some joints, such as proximal interphalangeal joints (PIPs), were grouped together.

Results

Total cohort of patients with JDM

The demographic and clinical data of 196 patients with JDM were obtained from 17 paediatric rheumatology centres (Table I). MRI was applied more than twice as often as biopsy to confirm JDM diagnosis. We further analysed the data of the 46 patients in our JDM cohort who received an MRI as well as a biopsy: both MRI and biopsy were pathological in 41 of these patients, and no patient with a pathological biopsy had a normal MRI. Apart from typical skin manifestations (99%) and muscle weakness or pain (95%), 27% of patients developed calcinosis over time, and nearly every tenth patient suffered from an ILD. Arthritis and/or joint contractures were found in 41% of the total cohort. After a mean disease duration of 5.1 years, the disease activity measured by PhGA was low, but approximately half of all patients still received methotrexate (MTX) and glucocorticoids.

MSA cohort

MSA testing was performed on 91 patients' sera. The characteristics of the MSA-tested patients did not differ significantly from those of the overall JDM cohort, except for an increased joint involvement rate of 67% compared to 41% in the overall JDM cohort. The majority of patients stated a Caucasian ethnicity (54/56), and two patients were of Asian ethnicity.

Patients in whom an MSA could be detected (Table I) had a shorter median disease duration (27 months, range 0–181) at the time of the antibody test compared to patients in whom no MSA was found (35 months, range 0–115), although this difference was not significant. We cannot exclude that MSA-negative patients had previously been

Table I. Patient characteristics of the total JDM cohort and the MSA cohort.

	JDM cohort n=196	MSA cohort n=88		*p*-value
		MSA+	MSA -	
Female, n (%)	137 (70.0)	25 (67.6)	39 (76.5)	0.355
Age at disease onset in years, mean (SD)	7.0 (3.6)	8.2 (3.8)	7.1 (3.4)	0.154
Time from first symptoms to first contact with paediatric rheumatologist in months, mean (SD)	5.3 (8.9)	3.9 (3.3)	3.7 (3.7)	0.771
Median (IQR)	3.0 (1.0-6.0)	3.0 (1.0-5.0)	2.5 (1.0-6.0)	
Number of patients with diagnostic procedures available for evaluation	n=166	n=37	n=51	
biopsy, n (% pathologic)	58 (87.9)	13 (86.7)	15 (93.8)	0.505
electromyography, n (% pathologic)	27 (92.6)	3 (100)	6 (100)	-
MRI, n (% pathologic)	126 (94.4)	27 (96.4)	34 (97.1)	0.872
Elevation of CK or other muscle-specific enzymes, n (% pathologic)	156 (91.0)	31 (86.1)	45 (91.8)	0.397
Characteristics at last documentation				
Disease duration in years, mean (SD)	5.1 (3.8)	5.2 (4.1)	4.2 (2.7)	0.393
Median (IQR)		4.5 (2.5-7.0)	4.0 (2.0-6.0)	
Patients with disease duration ≤2 years, n (%)	52 (26.5)	9 (25.0)	15 (30.0)	0.610
Age in years, mean (SD)	12.2 (4.0)	13.2 (3.6)	11.4 (3.9)	0.023
PhGA, NRS 0–10, mean (SD)	1.2 (1.9)	1.0 (1.5)	1.2 (2.0)	0.516
	n=176	n=28	n=41	
MMT8, range 0–80, mean (SD)	69.8 (18.8)	70.1 (21.6)	71.0 (14.2)	0.681
	n=137	n=12	n=15	
DAS, range 0–20, mean (SD)	4.5 (4.6)	3.2 (4.9)	4.0 (4.5)	0.379
	n=137	n=20	n=28	
Number of patients with specific therapies available for evaluation	n=185	n=37	n=51	
Patients with oral low-dose glucocorticoid treatment <0.2 mg/kg, %	26.0	32.4	31.4	0.916
Patients with oral high-dose glucocorticoid treatment ≥0.2 mg/kg, %	10.8	13.5	13.7	0.977
Patients with glucocorticoid pulse therapy in the last 12 months, %	11.9	8.1*	15.6*	0.289
Patients with conventional synthetic and biologic DMARDs, %				
Methotrexate	69.7	86.5	78.4	0.334
Hydroxychloroquine	45.7	51.4	52.9	0.883
Mycophenolate mofetil	27.7	43.2	29.4	0.180
Azathioprine	11.2	16.2	19.6	0.684
Cyclosporine A	7.0	13.5	3.9	0.101
Rituximab (in last 12 months)	5.3	5.4	0.0	0.093
Others	3.3	5.4	5.9	0.924
Intravenous immunoglobulins (in the last 12 months)	6.9	5.4	2.0	0.379
	20.3	24.3	29.4	0.597

Comparison of MSA cohort (n=88) to total cohort (n=196) in terms of demographic data, disease activity based on scores (PhGA, MMT, and DAS), diagnostic findings and therapy at last documentation.
PhGA: Physician's Global Assessment of Disease Activity; MMT8: manual muscle test 8; DAS: Disease Activity Score; CK: creatine kinase; DMARDs: disease-modifying anti-rheumatic drugs; IQR: interquartile range.
*number of patients with glucocorticoid pulse therapy in the last 6 months in the MSA cohort.

positive for an MSA at the earlier stages of the disease.

Distribution of MSAs

The MSA testing was performed on average two years after JDM diagnosis (median of 24.5 months, IQR 3.5–51.5). MSAs were identified in 40 of the 91 tested patients (44%), with anti-nuclear-matrix protein-2 (anti-NXP-2) and anti-transcription intermediary factor1γ (anti-TIF1γ) being the most common. The exact distribution is depicted in Figure 1. In three patients' sera, more than one MSA was found: anti-TIF1γ plus either anti-OJ, anti-signal recognition particle (anti-SRP) or anti-NXP-2. These patients were not included in Figure 1 and also excluded from the MSA subgroup analysis. Anti-small ubiquitin-like modifier activating enzyme (anti-SAE) was not identified in our cohort. A positive test result for MSAs as well as for MAAs was found in 9 patients, 7 out of 9 patients had an additional anti-Ro-52 (four times in combination with NXP2). MAAs were not taken into account for the phenotype characterisation of patients.

Phenotypes associated with MSAs

The clinical features of patients with specific MSAs are shown in Table II. The time from symptom onset to last follow-up differed between MSA subgroups. MMT was performed as part of the NPRD documentation, whereas CMAS was performed as part of routine clinical care, thus the time points for these two examinations differed. The lowest ever-recorded CMAS value was obtained on average one year, the lowest ever-recorded MMT value about two years (mean) after disease onset. The extent of muscle weakness evaluated by the Childhood Myositis Assessment Scale was significantly associated with an increased level of creatine kinase (r=-0.33; *p*-value 0.0175).

Significant differences between MSA subgroups were found in the occurrence

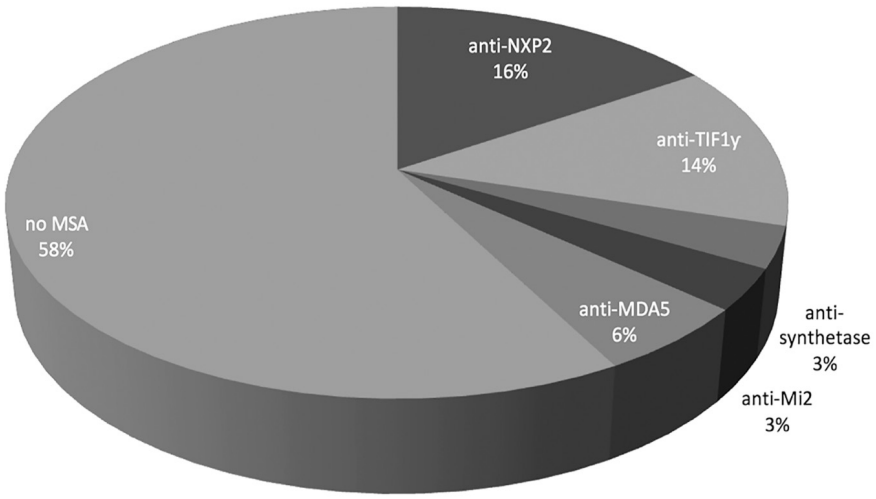

Fig. 1. Distribution of autoantibodies.
Here the distribution of a single MSA in JDM patients is depicted. Anti-synthetase antibodies include anti-Jo-1, anti-PL-7, anti-PL-12, anti-OJ and anti-EJ. Anti-SAE antibodies were not found in any patient. Patients double-positive for MSAs have not been included in the diagram.

of arthritis (p=0.02), fever (p=0.02), mucosal ulcers (p=0.014), and interstitial lung disease (p=0.018).

Anti-nuclear-matrix protein 2 antibody (anti-NXP-2)
At the onset of JDM, 21% of patients with anti-NXP-2 were younger than five years of age. Patients with anti-NXP-2 showed the lowest mean ever-recorded CMAS of all MSA subgroups. Dysphagia was documented most often in these patients compared to those with other MSAs (Table II). Almost half of all patients with anti-NXP-2 had CK levels elevated more than triple that of the normal range (Fig. 2).

Anti-transcription intermediary factor 1 γ antibody (anti-TIF1γ)
The mean of the lowest CMAS ever recorded was only mildly decreased in patients with anti-TIF1γ. In the vast majority of these patients, the CK level remained normal during the first 6 months of observation and the level of AST was not increased more than twice (Fig. 2).
Calcinosis occurred in 42%, joint involvement in one fourth of TIF1γ-positive patients showing polyarticular disease (Fig. 2b). The majority of patients (83%) had received IVIG, and 75% a combination of 2 DMARDs during the disease course (Table IV).

Anti-tRNA-synthetase antibodies (ASA)
We identified one patient with anti-Jo-1 and two patients with anti-PL-7 (Table II). Muscle strength was the least impaired based on CMAS scores in this group compared to the other MSA subgroups. Two patients showed high levels of CK, and all patients showed at least twofold elevated AST (Fig. 2). The lung function tests had been pathological in 2 of 3 patients, one of whom with anti-Jo-1 suffered from ILD.

Anti-melanoma differentiation-associated gene 5 antibody (anti-MDA-5)
Patients with anti-MDA-5 showed little impairment in muscle strength. In 60% of patients CK was not, but AST was more than threefold elevated (Fig. 2). All patients with anti-MDA-5 suffered from arthritis with the number of affected joints being highest of all MSA subgroups. Predominantly the small joints of the hands and feet were affected (Table III). Eighty percent of patients with anti-MDA-5 had fever and an impaired lung function, 60% had CT-confirmed ILD.

Anti-Mi-2
In patients with Mi2-antibodies, next to classic skin findings, muscle weakness was the central symptom of the disease, which was reflected in the lowest recorded mean values of CMAS and MMT, respectively. None had calcinosis. The CK levels in the first 6 months of observation were more than threefold elevated in all patients (Fig. 2).

Treatment and outcome of the MSA cohort
All patients in the MSA cohort received DMARDs during the disease course: MTX was used most often (96%), followed by hydroxychloroquine (59%), mycophenolate mofetil (23%), azathioprine (14%) and cyclosporine A (13%). The majority of patients also received glucocorticoid pulse therapy (85%) and IVIG (60%), and 14% were treated with biologics. Only 2 patients in the MSA cohort had received cyclophosphamide. DMARD combination therapy was prescribed to two-thirds of patients (Table IV). On average, patients with anti-MDA-5 received a combination therapy of two DMARDs four months, patients with anti-Mi-2 six months after disease onset. The other MSA subgroups were not treated with two DMARDs simultaneously during the first year of the disease.
Fifty percent of patients in the MSA cohort (33/66) showed a monocyclic course, 36% a chronic- progressive course (NXP-2: 70%, MDA-5: 25%) and 14% a multi-cyclic course. At the last assessment (mean disease duration of 4.7 years), the average disease activity of all patients in the MSA cohort according to the PhGA was 1.4±2.0 (highest in patients with anti-Mi-2, lowest in patients with anti-MDA-5). Fifty-one patients of the MSA cohort (56%) achieved an inactive disease state, but only 12/51 (23.5%) were off therapy.
At the last assessment, information on mobility was gathered for 71 patients. The mobility of one patient (with anti-TIF1γ) was limited to wheelchair use, and 6 patients had walking disabilities (one patient with anti-NXP-2, one with anti-TIF1γ and four without MSAs), but the majority of patients (70%) were able to participate in daily life without restrictions, even in sports classes.
Of the MSA cohort, one patient (1.1%) died due to lung involvement and severely affected laryngeal muscles, leading to aspiration pneumonia during

Table II. Clinical phenotypes of patients with a single myositis-specific antibody.

	All patients of MSA cohort n=88	Anti- NXP-2 n=14	Anti- TIF1γ n=12	Anti-Synthetase n=3	Anti- Mi-2 n=3	Anti- MDA5 n=5	No MSA detected n=51	*p*-value
Age at disease onset in years, mean (SD)	7.6 (3.6)	7.7 (4.5)	8.1 (2.9)	11.0 (5.6)	7.3 (1.5)	8.8 (3.8)	7.1 (3.4)	0.33
Patients <5 years at disease onset, n (%)	17 (19)	3 (21)	1 (8)	0 (0)	0 (0)	1 (20)	12 (24)	0.66
Disease duration at last follow-up in years, mean (SD)	4.7 (3.4)	7.7 (5.7)	5.4 (3.8)	2.0 (1.0)	4.0 (1.0)	3.6 (2.8)	4.2 (2.7)	0.41
Duration from symptom onset to diagnosis in months, mean (SD)	5.0 (10.9)	8.1 (15.5)	6.5 (13.9)	8.7 (10.8)	1.0 (1.0)	1.8 (1.8)	4.1 (9.4)	0.48
Lowest CMAS ever recorded, mean (SD)	35.2 (15.4)	27.3 (19.6)	40.7 (14.4)	46.0 (8.7)	30.3 (12.1)	44.3 (6.8)	35.0 (14.6)	0.35
n	n=69	n=11	n=10	n=3	n= 3	n=3	n=39	
Number of CMAS/person, mean (SD)	1.7 (1.1)	2.1 (1.3)	1.6 (1.1)	1.7 (0.6)	2.3 (0.6)	1.6 (1.5)	1.7 (1.2)	
Lowest MMT8 ever recorded, mean (SD)	61.3 (22.3)	57.2 (27.1)	57.7 (27.5)	80 (n. d.)	36.0 (32.7)	68.0 (13.9)	64.0 (19.4)	0.68
n	n=59	n=10	n=6	n=1	n=3	n=4	n=35	
Number of MMT8/person, mean (SD)	2.0 (1.8)	2.3 (2.1)	1.1 (1.6)	0.3 (0.6)	1.7 (0.6)	2.4 (1.5)	1.7 (1.9)	
Highest DAS ever recorded, mean (SD)	8.0 (4.4)	8.5 (3.7)	8.8 (5.5)	8.0 (n. d.)	8.7 (4.0)	6.2 (4.6)	7.9 (4.5)	0.82
n	n=71	n=12	n=10	n=1	n=3	n=5	n=40	
Number of DAS/person, mean (SD)	2.0 (1.8)	2.5 (2.0)	1.5 (1.3)	0.3 (0.6)	3.3 (0.6)	2.6 (1.3)	2.0 (1.8)	
Clinical parameters, n (%)								
Joint involvement (JI) ever	29 (33)	3 (21)	3 (25)	1 (33)	1 (33)	5 (100)	16 (31)	0.08
JI in the first 6 months of observation:	26 (31)	1 (8)	3 (25)	1 (33)	1 (33)	5 (100)	15 (31)	0.02
- Monarthritis	4 (5)	1 (7)	0 (0)	0 (0)	1 (33)	0 (0)	2 (4)	0.07
- Polyarthritis	14 (16)	0 (0)	3 (25)	0 (0)	0 (0)	4 (80)	7 (14)	0.10
Joint contractures	49 (56)	11 (79)	7 (58)	1 (33)	1 (33)	2 (40)	27 (53)	0.53
Dysphagia/dysphonia	21 (24)	6 (43)	0 (0)	1 (33)	1 (33)	0 (0)	13 (26)	0.20
Fever	18 (21)	2 (14)	1 (8)	1 (33)	1 (33)	4 (80)	9 (18)	0.03
Pathological lung function	21 (24)	1 (7)	2 (17)	2 (67)	0 (0)	4 (80)	12 (24)	0.02
Interstitial lung disease (verified by CT)	10 (11)	1 (7)	2 (17)	1 (33)	0 (0)	3 (60)	3 (6)	0.02
Calcinosis	23 (26)	5 (36)	5 (42)	0 (0)	0 (0)	1 (20)	12 (24)	0.48
Ulcers	19 (22)	3 (21)	2 (17)	1 (33)	0 (0)	3 (60)	10 (20)	0.42
Skin	10 (11)	2 (14)	2 (17)	1 (33)		0 (0)	5 (10)	0.57
Mucosa	9 (10)	1 (7)	0 (0)	0 (0)		3 (60)	5 (10)	0.01

Clinical presentation in different MSA groups: we refer to all clinical parameters that ever occurred during the course of the disease. CMAS: Childhood Myositis Assessment Scale (range 0–52); MMT8: manual muscle test 8 (range 0–80); DAS: Disease Activity Score (range 0–20); CT: computed tomography; MCP: Metacarpophalangeal joints; PIP: proximal interphalangeal joints; DIP: distal interphalangeal joints; MTP: metatarsophalangeal joints; nd: not determinable;

the observation period. This patient's serum had tested positive for anti-NXP-2, anti-PM-75 and anti-Ro-52.

Discussion

Our total cohort of 196 patients with JDM documented in the NPRD in Germany is comparable to other published international JDM cohorts in terms of demographic and disease characteristics, such as age at disease onset, female predominance, median time from symptom onset to diagnosis, and disease duration (5, 13, 14). Compared with our study, the large North American study of Shah *et al*. (13) which included 354 patients with JDM, found a less frequent occurrence of ILD (5%) and an increased rate of calcinosis in 34% of JDM patients, whereas the frequency of arthritis was comparable to our data. Similar findings were reported by Gowdie *et al*. (14), although the occurrence of calcinosis was only described in 18% of patients after a median follow-up of 4.0 years.

Comparing the demographic data, disease activity, clinical presentation and treatment of patients who were tested for MSAs with those of patients in the total JDM cohort, we found no relevant differences except for the occurrence of arthritis or joint contractures. Clinical manifestations associated with a more severe course of disease, such as ILD, occurred with equal frequencies in both cohorts.

Myositis-specific autoantibodies were detected in 40 (44%) of 91 tested JDM patients, with anti- NXP-2 and anti-TIF1γ being the most common. The prevalence of MSAs and their distribution remarkably resemble those of recent results in a large UK cohort of patients with juvenile inflammatory myopathies (5). Prior studies stated a similar distribution of anti-synthetase- and Mi2- antibodies, although with a higher percentage of anti-NXP-2 and anti-TIF1γ. (6, 15). These differences may be due to the fact that different analytical methods were used. Immunoprecipitation (IP) of proteins from radiolabelled K562 cells is considered the gold standard to detect most antibodies in myositis (16). IP requires a high effort, in terms of costs and technical capacities (16, 17) therefore, it is unlikely to be widely used in routine diagnostics. During the last years, commercial multiplex arrays have become established due to their simplicity and feasibility.

Cavanazza *et al*. compared line blot assays with IP and stated a good concordance for anti-TIf1γ, anti-MDA-5 and

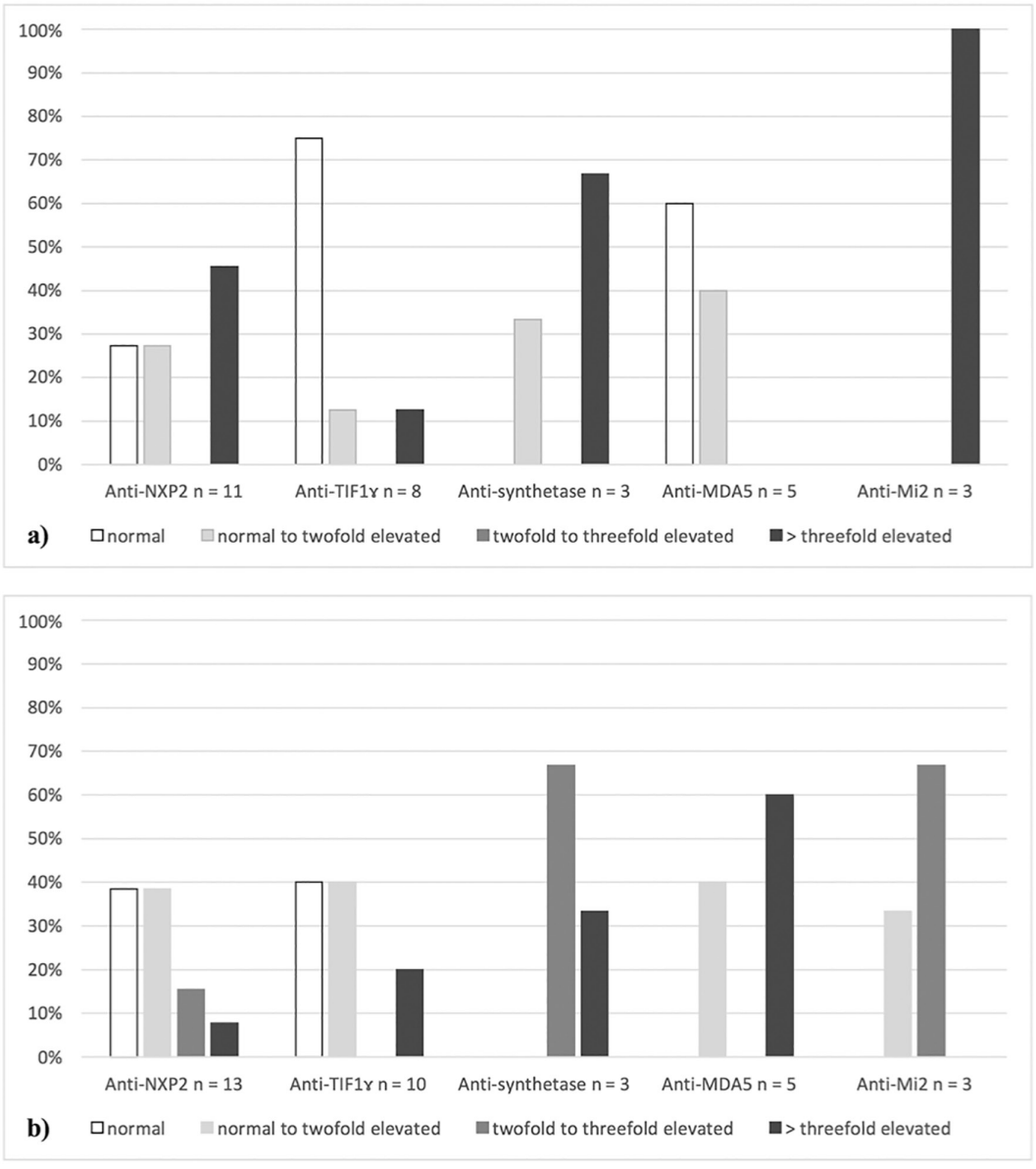

Fig. 2. CK and AST values in patients with specific MSAs. Percentage of patients with normal or elevated levels of a) creatine kinase (CK) and b) aspartate-aminotransferase (AST) in specific MSA groups. The displayed values of the CK and AST date from the first 6 months in specialised paediatric rheumatological care. If more than one value was available, the highest value was taken into account.

anti-NXP-2 detection, but a low sensitivity was found for anti-Jo-1 detection (17). Ghirardello *et al*. tested sera from 208 patients with IIM, 50 healthy subjects and 180 control patients (most of them had autoimmune diseases) both by a line blot assay and an in-house RNA immunoprecipitation and found that in-house testing yielded comparable results for the detection of anti-Jo1, anti-Pm/SCL and anti-Ku (specificity ranging from 96% to 100%), but it was more sensitive for the detection of anti-Mi2 and anti-synthetase-non-Jo-1 antibodies (12). The interpretation of two or more findings of an MSA in line blot assays might be difficult and was seen to be inconsistent with clinical features in adult patients (17). For this reason, three patients with multiple MSAs in our study were excluded from our evaluation.

In our study, a significant difference was observed in the prevalence of arthritis at disease onset as well as in the number of affected joints when comparing patients grouped according to MSA. In particular, patients with anti-MDA-5 often presented with polyarticular arthritis of the small joints of the hands and feet early in the disease course. Arthritis is significantly more common in these patients than in JDM patients with other or no myositis-specific autoantibodies. Although arthritis was less likely in patients with anti-TIF1γ, these patients tended to develop polyarthritis in small joints as well. Patients with anti-MDA-5 may be at risk of being misdiagnosed with polyarticular juvenile idiopathic arthritis, especially as they often show low-grade muscle involvement or are even amyopathic. On average, these patients showed a minor impairment in muscle strength and only a small increase in creatine kinase (CK) in our cohort. Also fever episodes at disease onset, mucosal ulcers and ILD were found to be common as described in the literature (5, 18-20). Further we also found the known association between lung involvement and anti-synthetase positivity whereby this association is more frequent in adult

Table III. Distribution pattern of arthritis in specific MSA subgroups.

	MSA cohort	Anti-NXP-2	Anti-TIF1γ	Anti- Synthetase	Anti-Mi2	Anti- MDA5	No MSA	*p*-value
Patients with arthritis, n	29	3	3	1	1	5	16	0.076
Number of ever-affected joints, mean (SD)	9.6 (9.3)	3.0 (1.7)	14.0 (12.3)	2.0 (n. d.)	1.0 (n. d.)	20.2 (12.3)	7.6 (6.1)	0.061
Number of affected joints in first 6 months, mean (SD)	2.8 (6.5)	0.3 (1.1)	3.5 (8.2)	0.7 (1.2)	0.3 (0.6)	14.2 (14.1)	2.4 (4.9)	0.018
Number of small joints affected in first 6 months, mean (SD)	2.0 (5.4)	0.3 (1.1)	3.0 (7.7)	0	0	11.6 (12.4)	1.4 (3.7)	0.013
Distribution pattern, n (%)								
Elbow joint	8 (28)	1 (33)	0 (0)	0 (0)	1 (100)	1 (20)	5 (31)	0.323
Wrist joint	11 (38)	0 (0)	2 (67)	0 (0)	0 (0)	2 (40)	7 (44)	0.517
Finger joints	MCP: 8 (28)	MCP: 1 (33)	MCP: 1 (33)	0 (0)	0 (0)	MCP:3 (60)	MCP: 3 (19)	0.636
	PIP: 13 (45)		PIP: 2 (67)			PIP: 5 (100)	PIP: 6 (38)	0.046
	DIP: 4 (14)		DIP: 1 (33)			DIP: 3 (60)		0.039
Hip joint	6 (21)	0 (0)	1 (33)	0 (0)	0 (0)	2 (40)	3 (19)	0.809
Knee joint	16 (55)	2 (67)	0 (0)	1 (100)	0 (0)	3 (60)	10 (63)	0.331
Ankle joint	10 (34)	0 (0)	2 (67)	0 (0)	0 (0)	2 (40)	46 (38)	0.425
Toe joints (MTP, DIP)	3 (10)	0 (0)	0 (0)	0 (0)	0 (0)	3 (60)	0 (0)	0.013

MCP: metacarpophalangeal joints; PIP: proximal interphalangeal joints; DIP: distal interphalangeal joints; MTP: metatarsophalangeal joints; nd: not determinable.

Table IV. Disease outcomes at last follow-up and therapy ever received in patients in specific MSA subgroups.

	MSA cohort n=88	Anti-NXP-2 n=14	Anti-TIF1 γ n=12	Anti-Synthetase n=3	Anti-Mi2 n=3	Anti-MDA5 n=5	No MSA n=51	*p*-value
Disease duration in years, mean ± SD	4.7 ± 3.4	7.7 ± 5.7	5.4 ± 3.8	2.0 ± 1.0	4.0 ± 1.0	3.6 ± 2.8	4.2 ± 2.7	0.41
PhGA, mean ± SD	1.4 ± 2.0	0.9 ± 1.1	1.8 ± 2.2	1.5 ± 0.9	2.2 ± 1.4	0.2 ± 0.3	1.4 ± 2.2	0.30
No. of patients to be evaluated	n=82	n=12	n=10	n=3	n=3	n=5	n=49	
Patients with PhGA ≤1, n (%)	51 (62.2)	8 (66.7)	5 (50)	1 (33)	1 (33)	5 (100)	31 (63.3)	0.31
No. of patients to be evaluated	n=82	n=12	n=10	n=3	n=3	n=5	n=49	
Patients with PhGA ≤1 and off therapy, n (%)	12 (23.5)	1 (12.5)	0	0	0	1 (20)	10 (32.3)	0.01
No.of patients to be evaluated	n=51	n=8				n=5	n=31	
CMAS, mean ± SD	46.9 ± 8.6	45.7 ± 10.0	50.3 ± 3.1	51.7 ± 0.6	46.5 ± 4.9	51.3 ± 1.2	45.6 ± 9.7	0.28
No. of patients to be evaluated	n=58	n=10	n=8	n=3	n=2	n=3	n=32	
MMT8, mean ± SD	70.6 ±17.5	69.4 ±24.1	57.5 ±31.8	-*	-*	80 ± 0	71.0 ± 14.2	0.65
No. of patients to be evaluated	n=27	n=7	n=2			n=3	n=15	
Patients without CK elevation, n (%)	54 (92)	7 (88)	5 (83)	-*	3 (100)	5 (100)	34 (92)	
No. of patients to be evaluated	n=59	n=8	n=6		n=3	n=5	n=37	0.29
Therapy ever received in %								
Methotrexate	95	93	100	100	100	80	96	0.12
Biologic DMARD	14	14	8	0	0	40	14	0.51
Combination of two DMARDs	51	14	75	33	33	60	57	0.06
Combination of three DMARDs	14	29	8	0	33	20	10	0.49
Pulse therapy with glucocorticoids	85	71	75	100	100	100	88	0.36
Intravenous immunoglobulins	60	64	83	33	33	60	57	0.55

Physician's Global Assessment of Disease Activity (PhGA), Manual Muscle Test 8 (MMT8), Disease Activity Score (DAS), creatine kinase (CK), disease-modifying anti-rheumatic drugs (DMARDs), *No data available.

patients with dermatomyositis than in children with jDM (6, 21): In two of three patients who were tested positive for anti-synthetase antibodies (2 x anti-PL-7, 1 x anti-Jo-1) in our study, the results of lung function tests were pathological; one patient (positive for anti-Jo1) was diagnosed with ILD and had typical mechanic`s hands.

In our cohort, calcinosis occurred in more than one-third of patients with anti-NXP-2 and anti- TIF1γ, much in parallel with other studies (6, 15, 22). In our patients with anti-NXP-2, further prominent clinical features were dysphagia and contractures (43% and 79% of patients), probably as a result of more severe muscle impairment, which

has also been described by Tansley *et al*. (22).

The degree of overall muscle affection was reflected in the scores of the MMT, CMAS and the level of CK. We found severe limitations in muscle strength, especially in patients with anti-Mi-2 and anti-NXP-2, who had the lowest mean CMAS values among all MSA subgroups. Limitations in muscle strength were accompanied by more than a threefold elevation in CK levels in all of the patients with anti-Mi-2 and in almost half of the patients with anti-NXP-2 in our cohort. Tansley *et al*. (5) also described increased muscle weakness in patients of the UK JDM cohort with anti-NXP- 2, anti-SRP and anti-Mi-2, compared with patients with other MSAs, based on CMAS scores. Rider *et al*. reported the highest levels of CK in US JDM patients with anti-Mi-2 and anti-SRP (6), while patients with anti-NXP-2 presented with intermediate levels of CK.

Since the benefit of MRI in assessing disease activity and damage has been demonstrated (23, 24), it has become increasingly important in confirming the diagnosis of JDM. In our cohort, MRI was used more than twice as often as muscle biopsy. This trend has also been described by Gowdie *et al*. (14) and McCann *et al*. (25), who showed that the increase in MRI examinations for diagnosing JDM was accompanied by a decrease in muscle biopsies performed.

All patients in the MSA cohort received DMARDs and oral glucocorticoids during the disease course. Prior studies indicated that patients with positive test results for some MSAs had been treated more aggressively than patients without MSAs (5). While treatment with cyclophosphamide was used more often in patients with TIF1γ antibodies in a large UK cohort (5), this was not the case in our cohort, where only two patients – who were MSA negative – received cyclophosphamide. In our study, there was no clear correlation between a more aggressive treatment and the presence of a distinct MSA. Biologic drugs were used both in patients with severe muscle weakness and in patients with mild muscle involvement (anti-NXP-2 and anti-MDA-5). The selection of drugs is still subject to local treatment experience because only limited evidence is available for treatment guidelines (26, 27). When analysing how often a combination of DMARDs – as an expression of intensified therapy – was used, we found that one-third of patients with anti-NXP-2 and anti-Mi-2 received up to three DMARDs concurrently during the disease course. Kishi *et al*. reported in their study of 320 patients with JDM enrolled in a North American registry that patients with TIF1γ antibodies received a greater number of major medications in combination than patients who were MSA-negative (28). In our study, patients with anti-MDA-5 and anti-Mi-2 received a combination of two DMARDs shortly after disease onset (four to six months later), whereas all other patients in the MSA cohort received the combination only one year after onset of the disease. However, patients also differed in their outcome, with the mean PhGA at the last follow-up (with comparable mean disease duration) being the highest (thereby worst) for patients with anti-Mi-2 and the lowest for patients with anti- MDA-5. One could conclude that not only the severity of the disease but also the response to therapy differs among the MSA subgroups. Additionally, it is also possible that the physician's assessment of disease activity was based more on skin or muscle involvement (the latter was more prominent in patients with anti-Mi-2 in our study as well as in the study by Tansley *et al*. [5]) than on other disease features, so that hypo- or amyopathic MDA-5 positive patients were better rated.

A limitation of our study was the retrospective, multi-centered design, which resulted in inhomogeneous or sometimes missing data. Furthermore, the number of patients in the MSA cohort was limited, with even smaller numbers in the different MSA subgroups. The first 6 months after diagnosis could have been a bit long to describe the onset of the disease. Since serum samples for the determination of MSAs were collected at different time points in the course of the disease, it is quite possible that some patients had a negative antibody status in our investigation even though they might previously had been positive for a specific antibody. Furthermore, the line-blot assay used in our study has been evaluated as suitable for the diagnostic workup in patients with myositis only in adults so far (11, 12). Therefore, we cannot exclude the possibility that more false-negative results occur in children and adolescents than in adult patients. We did not validate our results for MSA and MAA by another test like immunoprecipitation, another line blot (29) or ELISA (30). Nevertheless, both the distribution of the detected myositis-specific autoantibodies and the proportion of patients in whom they could not be detected are comparable to the results published by Tansley *et al*. (5), who used immunoprecipitation for MSA detection. Last, we were unable to analyse more recently developed outcome data, such as the 2016 ACR/EULAR criteria for minimal, moderate, and major clinical response in juvenile dermatomyositis (31), as these criteria were not available at the time of data collection for this study.

Conclusion

Diagnosing JDM remains challenging due to its heterogeneity, especially when disease-defining features such as proximal muscle weakness and typical skin lesions are less pronounced or even missing. Patients with JDM in Germany show a broad spectrum of clinical manifestations that can be grouped into homogeneous groups using MSA, which also help to predict the course and prognosis of the disease.

Acknowledgements

We are grateful to all patients and their parents for their participation in the NPRD.

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