The clinical features of juvenile dermatomyositis: A single-centre inception cohort

Paola Cancarini [a], Tomo Nozawa [c,d], Kristi Whitney [d,e], Audrey Bell-Peter [d], Jo-Anne Marcuz [d,e], Andrea Taddio [f], Jessica Guo [b], Saunya Dover [b], Brian M. Feldman [b,d,g,h,*]

[a] *Operative Unit of Pediatrics, ASST del Garda, Desenzano del Garda (BS), Italy*
[b] *Child Health Evaluative Sciences, Hospital for Sick Children Research Institute, Toronto, Canada*
[c] *Department of Pediatrics, Graduate School of Medicine, Yokohama City University, Yokohama, Kanagawa, Japan*
[d] *Division of Rheumatology, Department of Pediatrics, The Hospital for Sick Children, Toronto, Canada*
[e] *Department of Rehabilitation, The Hospital for Sick Children, Toronto, Canada*
[f] *Institute for Maternal and Child Health-IRCCS "Burlo Garofolo" and University of Trieste, Trieste, Italy*
[g] *Department of Pediatrics, Faculty of Medicine, University of Toronto, Toronto, ON, Canada*
[h] *Institute of Health Policy, Management & Evaluation, The Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada*

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ABSTRACT

Introduction: Juvenile Dermatomyositis (JDM), a severe and rare autoimmune disease, is the most common idiopathic inflammatory myopathy in children. We describe the clinical features of a large single-centre cohort.
Methods: We studied an inception cohort (0-18 years old) referred for diagnosis to the JDM clinic at The Hospital for Sick Children (SickKids), between January 1989 and September 2017. Probable or definite diagnosis of JDM was done according to the 2017 ACR/EULAR Criteria. We excluded children who had treatment started at another hospital. The data were collected retrospectively from clinical charts and the SickKids JDM database.
Results: 172/230 (74.8%) patients were included. They were most often female (female:male = 1.8:1); the age at diagnosis was 8.5±4.3 years. There was a positive family history for autoimmune disease in 52%, mainly rheumatoid arthritis. No patient died. The most common signs at inception were muscle weakness (85.5%), nailfold capillary abnormalities (83.4%), Gottron papules (78.5%), heliotrope rash (66.3%), abnormal gait (55.8%), and malar/facial rash (54.7%). The prevalence of Gottron papules, heliotrope rash, facial/malar rash, nailfold capillary abnormalities, Raynaud phenomenon, dysphonia/dysphagia (a frequent cause of hospitalization), mouth ulcers, calcinosis, eye problems, joint involvement, acanthosis nigricans and lipodystrophy increased during follow-up. Muscle enzymes, namely CK, ALT, AST, were often normal or only slightly raised despite active muscle disease; conversely LD was often high. Anti-Nuclear Autoantibodies were positive in 49.7% of patients at diagnosis. The course of the disease was: 29.1% monocyclic, 5.3% polycyclic, 33.1% chronic. The course of 56 patients (32.5%) was not classifiable due to length of follow-up. Corticosteroids were used as treatment in almost all our patients and 30% required intravenous therapy due to the severity of the presentation; methotrexate was added in 64%, more often in recent years. Unresponsive patients were treated mostly with intravenous immunoglobulins (IVIG).
Conclusions: The information obtained from this relatively large number of patients adds to the growing knowledge base of this rare disease.
Trial registration: SickKids Research Ethics Board approved the study.

Introduction

Juvenile Dermatomyositis (JDM) is an often-severe childhood autoimmune disease.

Pathologically JDM is a capillary vasculopathy primarily affecting muscles and skin with a pathognomonic rash; JDM can also affect internal organs, the gastrointestinal tract, lungs and cardiovascular system [1,2] potentially with severe consequences.

* Corresponding author at: The Hospital for Sick Children, 555 University Ave, Toronto, ON M5G 1X8, Canada.
E-mail address: brian.feldman@sickkids.ca (B.M. Feldman).

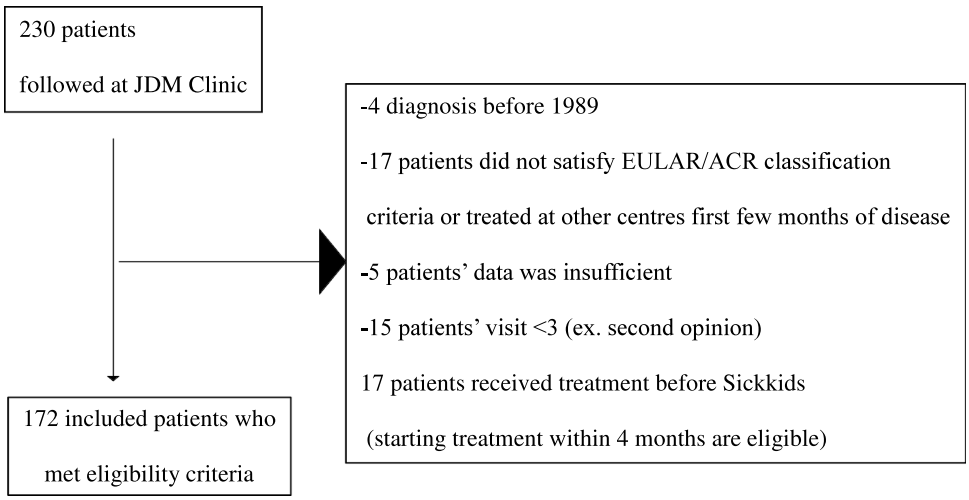


Fig. 1. Patient eligibility.

The etiology of JDM is uncertain. Likely, JDM results from genetic autoimmune susceptibility and response to an environmental trigger(s) such as an infectious agent, pollution, sun exposure or a medication [3–8].

JDM is a rare disease; the reported incidence ranges from 2.5 to 4.1 per million children per year [9]. However, it is the most common idiopathic inflammatory myopathy of childhood, accounting for about 85% of all cases [10].

As with all very rare diseases, the clinical features of JDM, its course, and prognosis, are still being explored. (10) [11].

We had previously reported the clinical features from our cohort of patients in Toronto [2]. With this paper, we extend our findings for an additional 15 years. This study analyzes the data of all JDM patients followed at The Hospital for Sick Children, Toronto (Sickkids), from January 1989 to September 2017. Our purpose was to add to the literature by investigating the main features of this disease – including demographic aspects, clinical features, initial symptoms, symptoms that developed during disease course, alterations of usual laboratory and functional tests, therapy, and outcomes.

Materials and methods

The patients in this study were all newly diagnosed (i.e., inception cohort) at Sickkids, and followed in its JDM clinic from January 1989 until September 2017.

The patients were eligible for the study if they met the following main criteria – diagnosis of JDM made at SickKids (or confirmed at SickKids immediately after diagnosis) from January 1989 until September 2017 at an age between 0 and 18 years, and regularly followed up at SickKids (i.e., not seen only for a second opinion).

Patients were seen by a multi-disciplinary team in the SickKids JDM clinic. Clinical, patient-reported outcome, and laboratory data were collected at each visit using a standardized data collection process and form.

Exclusion criteria were start of therapy at another centre, or other serious co-morbid conditions that would confound the results.

The diagnosis of JDM was reconfirmed for all the patients according to ACR/EULAR Rheumatology Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies (IIM), 2017 [12]. Both probable and definite diagnoses of JDM were included.

Data were collected by retrospective review of clinical charts and the JDM database, a clinical database maintained by the Division of Rheumatology, at SickKids. We consider disease inception, for the purpose of this study, as the period within the first 6 weeks following the initiation of therapy.

The data recorded were those at the inception of the disease (either outpatient or inpatient clinical records) and during each follow-up visit or hospitalization (until transition, at age 18, to the adult clinic); data were pooled and stored in a secure centralized electronic database, REDCap electronic data capture tools hosted at SickKids (https://projectredcap.org/software/), and de-identified prior to analysis.

The variables analyzed were as follows: age, sex, classification of JDM according to the criteria described above, classification as classic JDM, amyopathic/hypomyopathic dermatomyositis, or polymyositis, features of overlap syndromes, frequency of autoimmune disease in the family, number of follow-up visits and their frequency, disease flares, and course of the disease. We considered JDM families as having at least one member with an autoimmune condition if it was within their extended 3rd generation.

The course was classified as monocyclic (if the patient went into remission on therapy, was able to taper and discontinue treatment before 4.5 years, and there was no recurrence following therapy discontinuation until age 18), polycyclic (if the patients had flares of the disease with intervals without manifestations and without therapy) and chronic (if the therapy lasted more than 4.5 years and symptoms were drug dependent). By protocol, when our patients are clinically completely inactive, after 2 to 3 years, therapy (usually methotrexate) is slowly tapered and withdrawn over a period of months to years. As such, we used 4.5 years (at which point patients would have all been off therapy if tapering was successful) as the cut-off for our definition of monocyclic / chronic.

Other variables analyzed were symptoms (cardiovascular, respiratory and abdominal) and signs (heliotrope rash, Gottron's papules, skin ulcers, calcinosis, acanthosis, lipodystrophy, nail fold capillary changes by capillaroscopy), Raynaud phenomenon, other skin manifestations, eye involvement, lymph node enlargement, neurological manifestations, dysphagia or dysphonia, mouth ulcers, muscle weakness (using the Manual Muscle Testing scale: MMT) [13], muscle tenderness, contractures, joint involvement, and gait alterations.

Two validated functional scales for JDM were used – the Childhood Myositis Assessment scale (CMAS, normal score 52) [14] and the Child Health Assessment Questionnaire (CHAQ, 0 = normal physical function, 3 = very severe disability) [15]. For both scales, values at diagnosis as well as and the most extreme scores during the course (i.e., the lowest score for CMAS and the highest for CHAQ) were recorded.

The following laboratory tests were examined routinely at each visit: C-Reactive Protein (CRP), (coded as 0 if <0.1), erythrocyte sedimentation rate (ESR), creatine phosphokinase (CK), alanine transaminase (ALT), aspartate transaminase (AST) and lactate dehydrogenase (LD); their values at inception and the highest values during the course were

Table 1
Types of autoimmune disease present in the families of the patients studied.

Disease	Frequency	Percent
Rheumatoid arthritis	35	20.35%
Psoriasis	24	13.95%
Thyroiditis	20	11.62%
Inflammatory bowel disease	15	8.72%
Systemic Lupus Erythematosus	8	4.65%
Juvenile Idiopathic Arthritis	5	2.91%
Ankylosing spondylitis	3	1.74%
Diabetes Mellitus type I	2	1.16%
Scleroderma	2	1.16%
Celiac disease	1	0.58%
Dermatomyositis	1	0.58%
Vitiligo	1	0.58%
Guillain Barrè Syndrome	1	0.58%

recorded. Results of autoantibodies, if present, were also recorded as positive or negative; results of uncertain significance were considered negative with the exception of antinuclear antibodies (ANA) whose highest titre dilution was recorded.

Other tests analyzed comprised magnetic resonance imaging (MRI), electromyography (EMG), muscle biopsies and skin biopsies when available. Therapy at inception and during follow up was also recorded.

The SickKids Research Ethics Board approved the study.

Descriptive statistical analysis was done with Excel® (Microsoft Office 2016) and JASP Statistics® (JASP Team 2018, version 0.9). For continuous variables, with a normal distribution, mean and standard deviation are reported; for the other variables median and interquartile range (IQR). Categorical variables are reported as absolute value and percentage.

Complete case percent is the percent when missing data are excluded from the calculations.

A p-value < 0.05 has been considered as statistically significant.

Results

Between January 1989 and September 2017, 230 patients were followed in the JDM clinic; 172 (74.8%) of them were eligible for this study. Fifty-eight patients did not meet the entry criteria; four had the diagnosis made before January 1989, 17 patients did not satisfy EULAR/ACR classification criteria or were treated initially by other services, 5 patients had insufficient data, 15 patients had fewer than 3 visit at SickKids (these were "second opinions") and 17 patients had received treatment for more than 16 weeks before they came to SickKids. One patient had been transferred to another hospital within 6 weeks from diagnosis; he is included in the inception period analysis but not in the follow-up analysis. (Fig. 1).

Of the 172 enrolled patients, 110 (63.9%) were female. The age at the diagnosis was 8.5±4.3 years, (range of values [ROV] 1.7 to 17.9 years).

One hundred sixty-four (95.3%) patients had definite JDM and 8 (4.6%) probable.

One hundred fifty-eight (91.8%) had classical JDM; 7 (4.1%) were classified as amyopathic JDM, 2 (1.2%) hypomyopathic JDM and 5 (2.9%) polymyositis. Two (1.2%) patients developed overlap features of scleroderma. The course of the disease was monocyclic in 50 (29.0%), polycyclic in 9 (5.2%), chronic in 57 (33.1%) and not classifiable in 56 (32.6%) because of insufficient follow up. Not considering unclassifiable patients, the proportion of monocyclic, polycyclic and chronic course becomes 43.1%, 7.7% and 49.1% respectively.

Visits and hospitalizations

The patients had a median of 21 visits (IQR 13–39). The median

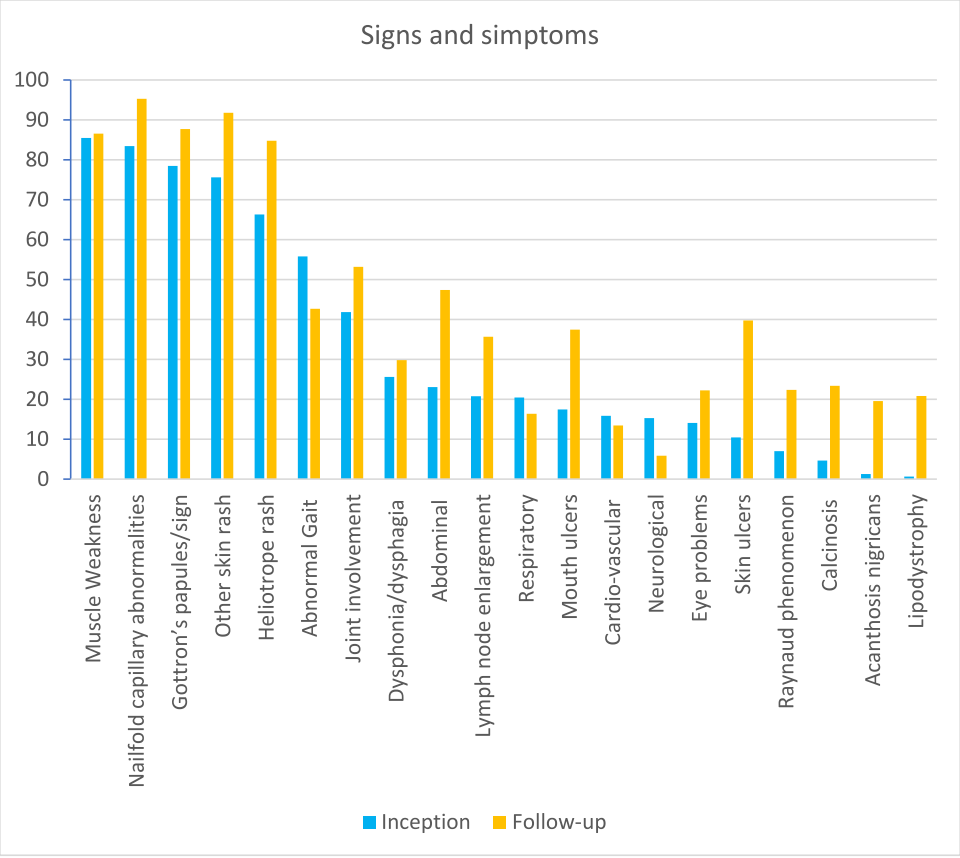


Fig. 2. Frequency of signs and symptoms in the patients studied (in percent) comparing the first six weeks and the following period.

Table A.I
Signs and symptoms at inception and during follow-up.

Signs and symptom	Inception			Follow up		
	Tested	**Positive**	**Complete case %**	**Tested**	**Positive**	**Complete case %**
Skin						
Nailfold capillary abnormalities	169	141	83.4	170	162	95.3
Gottron's papules/sign	172	135	78.5	171	150	87.7
Heliotrope rash	172	114	66.3	171	145	84.8
Other skin rash	172	130	75.6	171	157	91.8
Facial/Malar rash	*172*	*94*	*54.7*	*171*	*111*	*64.9*
Widespread rash (only)	*172*	*0*	*0.0*	*171*	*3*	*1.8*
Widespread and malar rash	*172*	*25*	*14.5*	*171*	*22*	*12.9*
Shawl rash	*172*	*7*	*4.1*	*171*	*14*	*8.2*
Non-specified skin symptoms	*172*	*11*	*6.4*	*171*	*45*	*26.3*
Poikiloderma	*172*	0	*0.0*	*171*	*5*	*2.9*
Alopecia	*172*	2	*1.2*	*171*	*4*	*2.3*
Skin ulcers	172	18	10.5	171	68	39.8
Acanthosis nigricans	156	2	1.3	169	33	19.5
Muscle						
Weakness (MMT<68/70)	172	147	85.5	171	148	86.5
Tenderness	154	55	35.7	171	71	41.5
Contractures	166	36	21.7	171	45	26.3
Joint involvement	172	72	41.9	171	91	53.2
Abnormal Gait	172	96	55.8	171	73	42.7
Dysphonia/dysphagia	172	44	25.6	171	51	29.8
Swallowing problems	172	13	7.6	171	12	7.0
Nasal voice	172	4	2.3	171	9	5.3
Swallowing problems and nasal voice	172	5	2.9	171	10	5.8
Dysphonia/dysphagia scored, but specific features not recorded	172	22	12.8	171	19	11.1
No problem noted	172	128	74.4	171	121	70.8
No data		0			1	
Lymph node enlargement	159	33	20.8	171	61	35.7
Cervical	159	12	7.5	171	36	21.1
Axillary	159	2	1.3	171	4	2.3
Inguinal	159	1	0.6	171	0	0.0
Submandibular	159	1	0.6	171	1	0.6
Widespread	159	6	3.8	171	13	7.6
Nonspecific site	159	11	6.9	171	7	4.1
No enlargement	159	127	79.9	171	109	63.7
No data		*12*			2	
Mouth ulcers	172	30	17.4	171	64	37.4
Abdominal	169	39	23.1	171	81	47.4
Pain	169	18	10.7	171	53	31.0
Hepatomegaly	169	13	7.7	171	11	6.4
Diarrhea	169	3	1.8	171	24	14.0
Bleeding	169	2	1.2	171	6	3.5
Splenomegaly	169	3	1.8	171	2	1.2
Nausea	169	2	1.2	171	22	12.9
Reflux	169	0	0.0	171	4	2.3
Duodenal ulcer	169	1	0.6	171	0	0.0
Nonspecific symptoms	169	7	4.1	171	7	4.1
Eosinophilic esophagitis	169	0	0.0	171	1	0.6
Acute appendicitis	169	0	0.0	171	0	0.0
Acute cholecystitis	169	0	0.0	171	0	0.0
No symptoms	169	130	76.9	171	90	52.6
No data		3			1	
Calcinosis	172	8	4.7	171	40	23.4
Eye problems	156	22	14.1	171	38	22.2
Dry eye	156	1	0.6	171	0	0.0
Blurry vision	156	2	1.3	171	1	0.6
Photophobia	156	1	0.6	171	1	0.6
Blepharitis	156	1	0.6	171	0	0.0
Cataracts	156	0	0.0	171	20	11.7
Conjunctivitis	156	2	1.3	171	4	2.3
Diplopia	156	1	0.6	171	0	0.0
Exophthalmos	156	1	0.6	171	0	0.0
Redness	156	2	1.3	171	4	2.3
Papilledema	156	0	0.0	171	1	0.6
Glaucoma	156	0	0.0	171	1	0.6
Nonspecific symptoms	156	11	7.1	171	7	4.1
No symptoms	156	134	85.9	171	133	77.8
No data available		16			1	
Cardiovascular	170	27	15.9	171	23	13.5
Cardiomegaly	170	0	0.0	171	2	1.2
Hypertension	170	1	0.6	171	3	1.8
Systolic murmur	170	13	7.6	171	12	7.0
Tachycardia	170	5	2.9	171	8	4.7

(*continued on next page*)

Table A.I (*continued*)

Signs and symptom	Inception			Follow up		
	Tested	**Positive**	**Complete case %**	**Tested**	**Positive**	**Complete case %**
Pericardial effusion	170	0	0.0	171	0	0.0
Mitral valve prolapse	170	0	0.0	171	1	0.6
Pericardial tamponade	170	0	0.0	171	1	0.6
Nonspecific symptoms	170	10	5.9	171	1	0.6
No symptoms	170	141	82.9	171	148	86.5
No data available		2			1	
Raynaud phenomenon	172	12	7.0	170	38	22.4
Respiratory	171	35	20.5	171	28	16.4
Cough	171	5	2.9	171	18	10.5
Chest pain	171	3	1.8	171	4	2.3
Atelectasis	171	7	4.1	171	4	2.3
Subcutaneous emphysema / pneumomediastinum	171	1	0.6	171	0	0.0
Interstitial lung disease	171	4	2.3	171	2	1.2
Pneumonia	171	3	1.8	171	1	0.6
Restrictive lung disease	171	5	2.9	171	0	0.0
Reactive airways disease	171	2	1.2	171	0	0.0
Shortness of breath	171	7	4.1	171	2	1.2
Pulmonary emphysema	171	0	0.0	171	0	0.0
Bronchial asthma	171	0	0.0	171	0	0.0
Nonspecific symptoms	171	9	5.3	171	2	1.2
No symptoms	171	136	79.5	171	143	83.6
No data available		1			1	
Neurological	144	22	15.3	171	10	5.8
Cranial nerve neuropathy	144	0	0.0	171	0	0.0
Decreased deep tendon reflex	144	3	2.1	171	1	0.6
Dizziness	144	0	0.0	171	1	0.6
Headaches	144	1	0.7	171	2	1.2
Incoordination	144	1	0.7	171	0	0.0
Lethargy	144	2	1.4	171	0	0.0
Tremor	144	0	0.0	171	2	1.2
Psychosis	144	1	0.7	171	0	0.0
Nonspecific symptoms	144	15	10.4	171	4	2.3
No symptoms	144	122	84.7	171	161	94.2
No data available		28			1	
Lipodystrophy	159	1	0.6	168	35	20.8

follow-up was 5.75 years (IQR 2.30-10.08). Median duration from earliest symptom onset to diagnosis was 3.0 months (IQR 1.6–6.2).

Family history

Family history of autoimmunity was present in 89/172 patients (51.74%); the diseases recorded are described in Table 1 – the most common being rheumatoid arthritis in 35 (20.35%), followed by psoriasis in 24 (13.95%).

Signs and symptoms

The frequency of signs and symptoms separated by presentation (the first six weeks) and accumulated during the followup period are shown in Fig. 2. Table A.I displays this information in more detail.

Nailfold capillary abnormalities 141 (83.4%), Gottron's papules 135 (78.5%) and heliotrope rash 114 (66.3%) were the most frequent signs/symptoms involving skin/adnexa, however facial/malar rash was present in over half. Skin ulcers occurred in 18 (10.5%) patients at inception and 68 (39.8%) at some point during follow up; while sometimes severe, in some these were mild and superficial. Calcinosis was seen in 40 of 171 (23%) of our patients at some point. Over time calcinosis resolved in 17 of these 40.

Weakness was the most frequent symptom occurring in 147 (85.5%) in the inception period; 1 patient who was initially strong subsequently developed weakness.

Joint involvement (arthritis) affected 72 (41.9%) at inception and was seen in 91 patients (53.2%) during follow-up. Dysphonia and dysphagia occurred in about 1/4 of the patients. Lymph node enlargement was reported in 1/5; the size of node enlargement was rarely specified in the charts.

Abdominal symptoms were usually non-specific – the most frequent was abdominal pain and was present in 18 (10.7%) at inception and 53 (31.0%) during follow-up.

Evaluation scales

At each follow-up visit, patients were asked to complete the CHAQ. At inception the CHAQ (n = 124 patients) median score was 1.125 (IQR 0.375-–1.750).

The CMAS was scored by a trained physiotherapist at every visit since the scale was developed. At inception the median value was 31.0 (IQR 15.0–43.0).

Laboratory tests

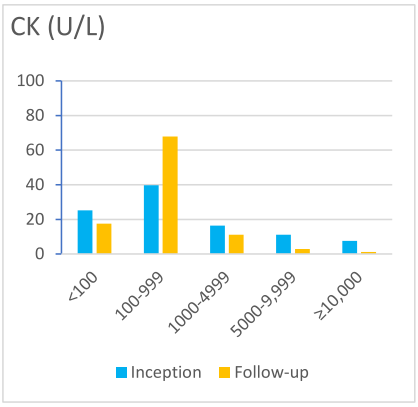
Fig. 3 shows the values of CK, LD, AST, and ALT comparing the inception period and the highest values seen during followup. Details are presented in Table A.II. Elevated LD was slightly more sensitive at inception than the transaminases.

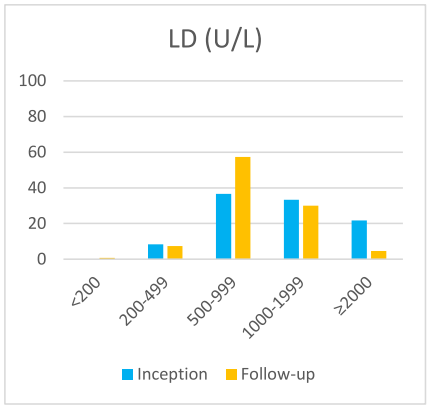
Inflammatory markers were elevated in under half the patients at inception.

Autoantibodies

ANA was positive ($\geq$ 1/160) in 77/155 (49.6%) at inception (Table A.III).

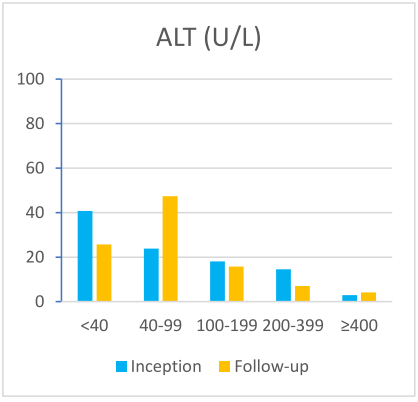
While all current patients are tested at inception for myositis specific- and myositis-associated autoantibodies, historically, testing was rarely done, and a variety of testing laboratories and assays were used. 85 patients had MSA testing (2 positive), and 32 had MAA testing (2 positive).

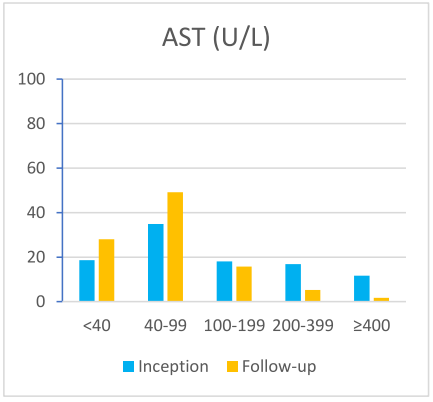




	Inception	Follow-up
Median	327.0	180.0
IQR	99.5, 3247.5	114.5, 464.0

	Inception	Follow-up
Median	1117.0	823.5
IQR	756.2, 1873.0	628.8, 1128.8





	Inception	Follow-up
Median	54.5	57.0
IQR	29.0, 135.5	39.0, 114.0

	Inception	Follow-up
Median	88.0	54.0
IQR	44.0, 219.2	38.0, 87.5

Fig. 3. Graphic representation of the frequency classes of CK, LD, AST, ALT (in percent) comparing the first six weeks and the following period.

Imaging tests and biopsies

MRI was the most sensitive marker for myositis (positive in 90%) and was done in the majority of patients (all patients seen in recent years). Some patients were seen before MRI was widely available; of 31 subjects with no baseline MRI, 11 (9 abnormal) had an MRI during the follow-up period, as the test became available. A small number of subjects had a second follow-up MRI. Table A.IV shows the positivity rates for MRI, EMG, skin and muscle biopsies.

Therapy

Corticosteroids were used in almost all patients at therapy initiation. Table 2, and Fig. 4 present the therapies used during the inception phase and follow-up; many different combinations of agents were used, although the majority were treated with oral prednisone with methotrexate. Additional agents were added over time as necessary; the maximum number of therapies used by any one patient was 10.

Changes by decade

We examined changes in several variables by decade of presentation to look at the change in presentation, and the potential effect of practice change.

We did not have initial CHAQ and CMAS scores for the 4 patients who presented in the 1980s. The median CHAQ for those presenting in the 1990s was 1.19; the CMAS (developed late in the 1990s) was just scored in 1 patient at presentation (score of 52). The median CHAQ score for those presenting in the 2000s was 1.0 and was 1.125 for those presenting in the 2010s. The corresponding median CMAS was 29.5 and 31.

Medication practices appeared to change slightly over the decades. The 4 patients in this series who presented in the 1980s, were all treated with systemic corticosteroids and all were treated with methotrexate and all, during the course of their illness, were treated with IVIG. Of 54 patients who presented in the 1990s, 5 with mild disease were not treated with systemic corticosteroids (only treated with topical medications and/or hydroxychloroquine), 24 were treated with MTX, and 22 with IVIG. Of 63 patients who presented in the 2000s, 3 with only mild skin disease were not treated with corticosteroids, 59 were treated with MTX, and 29 with IVIG. Of 51 patients presenting between 2010 and 2017, 6 with mild skin disease were not treated with systemic corticosteroids, 45 were treated with MTX, and 19 were treated with IVIG.

Disease course was 25% monocyclic and 75% chronic in those presenting in the 1980s, 39% monocyclic and 28% chronic in those from the

Table A.II
Results of laboratory tests.

	At inception		Highest value at follow up	
	n	%	n	%
CRP mg/dl	69		74	
<1	40	58.0	23	31.1
1–9	22	31.9	43	58.1
≥10	7	10.1	8	10.8
ESR mm/h	171		170	
Normal to moderately elevated (<40)	134	78.4	96	56.5
Highly elevated (≥40)	37	21.6	74	43.5
CPK (U/L)	171		171	
<100	43	25.1	29	17.5
100-999	68	39.8	116	67.8
1000-4999	28	16.4	19	11.1
5000-9999	19	11.1	5	2.9
≥10000	13	7.6	2	1.2
ALT (U/L)	172		171	
<40	70	40.7	44	25.7
40-99	41	23.8	81	47.4
100-199	31	18.0	27	15.8
200-399	25	14.5	12	7.0
≥400	5	2.9	7	4.1
AST (U/L)	172		171	
<40	32	18.6	48	28.1
40-99	60	34.9	84	49.1
100-199	31	18.0	27	15.8
200-399	29	16.9	9	5.3
≥400	20	11.6	3	1.8
LDH (U/L)	120		150	
<200	0	0.0	1	0.7
200-499	10	8.3	11	7.3
500-999	44	36.7	86	57.3
1000-1999	40	33.3	45	30.0
≥2000	26	21.7	7	4.7

Table A.III
Titer and pattern of Anti-Nuclear Antibodies (ANA).

Test	At inception			Highest value at follow up		
	n	%	Complete case %	n	%	Complete case %
Titer	172			172		
>1/1280	6	3.5	3.9	1	0.6	2.9
1/1280	29	169	18.7	8	4.7	23.5
1/640	23	13.4	14.8	3	1.7	8.8
1/320	13	7.6	8.4	3	1.7	8.8
1/160	6	3.5	3.9	5	2.9	14.7
1/80	4	2.3	2.6	2	1.2	5.9
1/40	34	19.8	21.9	6	3.5	17.6
Negative	40	23.3	25.8	6	3.5	17.6
Missing	17	9.9		138	80.2	
Pattern	172			172		
Homogeneous	8	4.7	7.9	3	1.7	12.5
Homogeneous nucleolar	2	1.2	2.0	1	0.6	4.2
Nucleolar	2	1.2	2.0	0	0.0	0.0
Speckled	69	40.1	68.3	17	9.9	70.8
Speckled homogeneous	19	11.0	18.8	3	1.7	12.5
Speckled nucleolar	1	0.6	1.0	0	0.0	0.0
Missing	71	41.3		148	86.0	

1990s (20% not classifiable as they were not followed long enough to meet our definitions), 33% monocyclic and 49% chronic (14% not classifiable) in those from the 2000s, and 14% monocyclic and 8% chronic (71% not classifiable) in those from the 2010s. Polycyclic disease, by decade of presentation, was seen in 0, 13, 3 and 0%.

Table A.IV
Imaging and electrophysiology tests and biopsies. Some patients had follow-up testing done as their clinical course warranted.

Exams	Inception				Follow-up			
	Patients tested		Positive		Patients tested		Positive on at least one repeated test	
	N°	%	N°	%	N°	%	N°	%
MRI	130	75.6	117	90.0	55	32.0	38	69.1
EMG	115	66.9	96	83.5	13	7.6	9	69.2
Muscle biopsy	60	34.9	51	85.0	2	1.2	1	50.0
Skin biopsy	25	14.5	18	72.0	6	3.5	5	83.3

Discussion

We report on the features and course of 172 JDM patients followed over a period of 38 years at a single centre, following a standardized reporting protocol.

Our study adds to a growing literature examining the clinical features of childhood myositis. For example, recent series focusing on clinical features have been published from Thailand in 2001 [16], India in 2013 [17] and Turkey in 2016 [18]; these studies reviewed a shorter period of time and reported on fewer patients: 7, 18 and 50 respectively. Studies following patients for longer periods of time have been reported from Australia 1989-2010 [19] and Missouri 1988-2010 [20] (57 and 78 patients respectively). In 2014, a large study reported the data of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Legacy Registry [21] studying 384 patients, followed for 2 years (2010–2012), from 55 American pediatric rheumatology centers. Our series adds to this literature.

Our cohort has been followed at a single centre, by the same multispecialty team, and using the same data collection tools, so has had a uniform approach both to diagnosis and therapy (by following the same schedule for visits, reports, laboratory and diagnostic tests, etc.).

In our study, the ratio of female to male patients is in line with the majority of other studies [21], although a British study reported a higher ratio of 5:1 [22]. Our average age at diagnosis, in keeping with other studies, showing a peak incidence within the reported ranges of 5 to 10 years of age [9,23].

The course of the disease in our patients is quite similar to our previous reports [2,24], and similar to that reported by other centers [4]. However, in one study done in Melbourne, the number of patients with polycyclic disease was considerably higher at 17.7% [8,19]. This likely reflects a difference in the way the term has been defined; for our definition we require a period of greater than 12 weeks in clinical and laboratory remission while off all medications before relapse.

A family history positive for autoimmune disease was seen in a greater proportion than observed in the CARRA Registry (23%) [21]; however, that paper did not specify how many degrees of relatives were taken into account. Our proportion is similar to that reported in some other studies, e.g., in the study of Niewold et al. [3] the percentage was 51%. That study considered JDM families as having at least one member with an autoimmune condition if it was within their extended 3rd generation, as did we.

Among our patients, the most frequent autoimmune disease in the family was rheumatoid arthritis which is similar to the Niewold study (15.79%) [3]; this seems to be a consistent finding of a higher risk than the general population.

The Niewold study [3] found an important correlation with relatives affected by SLE and Diabetes Mellitus type 1, which was not seen to the same degree in our cohort (Table 1). It is possible that differences in methods (we acquired family history at diagnosis) account for the discrepancy.

Clinical signs and symptoms in our cohort appear to be similar, for the most part, to many of the other series [18–21]. However, among

Table 2
Therapy at inception and during follow-up.

Therapy		At inception (N=172)		Follow up (N=171)	
		Frequency	Percent	Frequency	Percent
Corticosteroids	Oral prednisone	156	90.7	na	na
	Intravenous Methylprednisolone	53	30.8	32	18.7
	Hydrocortisone topical	7	4.1	7	4.1
	Betamethasone topical	10	5.8	9	5.3
	Fluocinonide	2	1.2	2	1.2
Immunoglobulin IV	IVIG	27	15.7	72	42.1
	Methotrexate	110	64.0	131	76.6
Immunosuppressants	Cyclophosphamide	4	2.3	12	7.0
	Hydroxychloroquine	8	4.7	36	21.1
	Chloroquine	0	0.0	1	0.6
	Cyclosporine	2	1.2	14	8.2
	Mycophenolate mophetil	0	0.0	9	5.3
	Leflunomide	0	0.0	9	5.3
	Azathioprine	1	0.6	6	3.5
	Pimecrolimus topical	0	0.0	3	1.8
	Tacrolimus topical	15	8.7	29	17.0
Anti-inflammatory	Indomethacin	2	1.2	4	2.3
	Rofecoxib	2	1.2	1	0.6
	Naproxen	15	8.7	20	11.7
Monoclonal antibodies	Infliximab	0	0.0	1	0.6
	Etanercept	0	0.0	1	0.6
	Rituximab	0	0.0	10	5.8
Others	Oxygen	1	0.6	2	1.2
	Topiramate	0	0.0	2	1.2

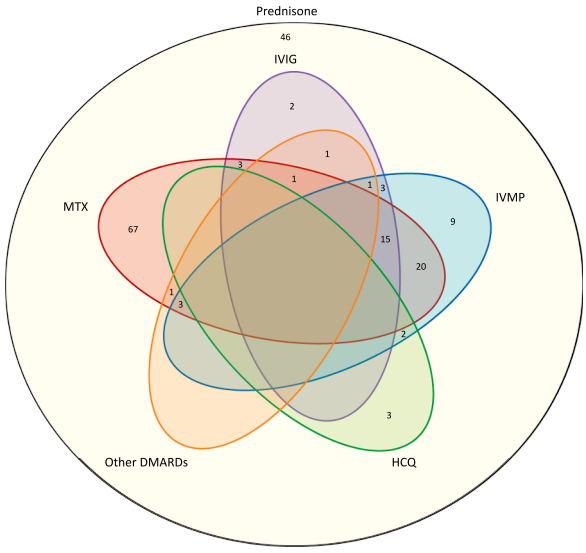


Fig. 4. Venn diagram of the initial therapies used in this cohort of patients. MTX = methotrexate, IVMP = high dose intravenous methylprednisolone, IVIG = intravenous immunoglobulin, HCQ = hydroxychloroquine, DMARDs = disease modifying anti-rheumatic drugs (cyclophosphamide, n=5, azathioprine, n=1, cyclosporine A, n=1).

these studies there is a large difference in the frequency of nail fold capillary abnormalities; in our study it was the second most common sign at diagnosis whereas at the Royal Children Hospital of Melbourne [19], it was seen in only 68%. Using more sophisticated microscopy in a study setting, we have found that all children with the dermatomyositis phenotype have at least reduced nailfold capillary density [25].

Not surprisingly, clinical features whose frequency increased during the follow-up period were scarring features of the disease – calcinosis, lipodystrophy, and acanthosis nigricans (representing, most likely, insulin resistance) – but features related to medication side-effects like eye problems and mouth ulcers also increased in frequency during the follow-up period.

Calcinosis is understandable because it is usually a complication that appears during the evolution of the disease – likely a scarring reaction due to chronic inflammation [2]; this trend has been reported also by Robinson et al. [21]. Although calcinosis has long been thought to represent scarring [26], a small number of our patients presented with calcinotic lesions; these patients had chronic atrophic skin lesions as well, and likely had longstanding disease at the time of presentation.

As far as the eye problems are concerned, cataracts occurred during the long-term course as a likely consequence of long-term therapy with corticosteroids [27].

Joint involvement (almost always arthritis) was usually polyarticular; it was present in in over half of our patients during the inception and/or follow-up periods. This is similar to our previous study [28], but somewhat more prevalent than in the Melbourne series [19].

Clinically apparent cardiovascular involvement was very rare in our population, as in the literature; the true incidence of cardiac disease during active JDM is unknown and its relationship with JDM seems, perhaps, not to be specific [29,30]. Subclinical cardiovascular disease may be more prevalent overall when age increases [31], perhaps more similar to the adult population with Dermatomyositis (DM) [32].

Pulmonary involvement appears to be much less common in children with JDM than in adults [33]. One of the important pulmonary complications is a reduction in ventilatory capacity [33]; significant restrictive lung disease was present in very few of our patients at inception and none during follow up (likely because of aggressive therapy). Poor chest wall compliance, likely due to weak respiratory muscles rather than interstitial lung disease, seems to be the most common pulmonary finding and, to a milder degree, was present in many of our patients.

Muscle enzyme tests were often normal in our patients despite active muscle disease, data not significantly different from those presented in the literature [20,34]. LD was the most frequent laboratory abnormality we found. Similar results with the percent of abnormal LD being higher than CK, ALT, and AST were found by Gowdie at al. [19].

Among autoantibodies, ANA was positive often; similar findings were also found in the literature, with a rate of positivity of 63% [19].

Myositis-specific autoantibodies (MSAs) were tested very rarely in this cohort due to lack of availability, and due to the high frequency of immunoprecipitation bands of unknown specificity in our early study

[35]. Like at many centres, now that there are commercially available immunoblot assays, we are testing all new patients for MSA and Myositis-associated antibodies (MAA).

The results of our other muscle directed tests are similar to previous series. In our cohort, muscle biopsy was done frequently until the mid-1990s. Now we reserve biopsy for cases with no skin rash, or unusual features, to confirm diagnoses. In our cohort biopsy was positive in most patients, similar to other studies [21]. EMG was also done often, with a reasonable sensitivity. This test can be helpful in making a diagnosis, but it is invasive and, like biopsy, we now reserve it only for uncertain cases [36]. MRI, in our cohort, was more sensitive and less invasive; it is our preferred test at this point. Similar results have been observed in other studies [21,37].

Corticosteroid therapy has been in widespread use for JDM since the 1970s [23,38] and, in our cohort Methotrexate (MTX) has been regularly used, at the outset, as a steroid-sparing agent since 1997 [4,39]. This explains the difference in number of patients treated with corticosteroids and MTX in our series. The earliest patients used only corticosteroids as therapy, and only later was MTX routinely given as a steroid-sparing agent. Similar results were founds also by Gowdie at al. [19] who, like us, analyzed a cohort of patients starting in 1989.

Our findings should be interpreted considering potential limitations. Although data was collected at every visit and onto standardized data collection forms for this purpose, this is still a retrospective study and some data is missing, and some is likely imprecise. However, our study team remained largely constant over the period of study, and patients were evaluated by clinicians and experienced physiotherapists at every visit; we believe our findings are likely more consistent that what has been reported in some international registries. Additionally, our study analyzed patients between 1989 and 2017; in that period many innovations have occurred, and disease outcome appears to have improved. Our study analyzes patients from a single center, so its results may not generalize to the whole JDM population – especially those in countries that lack resources and may experience a different course of disease. Finally, this research was done in a pediatric center – the patients could only be followed-up until the age of 18 years – so the very long-term evolution of the disease and the outcome of these patients could not be discerned.

JDM is rare; as such, it is of considerable importance to fully understand its presenting features and evolution. Our cohort, in many respects, confirms the findings seen in previous studies and, therefore, adds to the precision of our knowledge about clinical manifestations of JDM. There are areas in which our cohort differs from what has been reported, and these are areas that should be targeted in future research.

Conclusions

JDM is a rare disease, and the findings from our long-term cohort study add to the growing body of knowledge on the clinical characteristics, care, and optimal management of these patients.

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Ethics

Ethical approval was obtained by the Hospital for Sick Children Research Ethics Board (Protocol number 1000019708).

Data sharing statement

Currently there are no plans to share additional data beyond what is included in this article.

Declaration of Competing Interest

T. Nozawa: Scholarships from Japan Society of Allergology and Gushinkai, Fellowship from Mochida Memorial Foundation; Advisory Board member for Bristol Myers Squibb Company. The remaining authors have no competing interests to declare.

Appendix

Tables A.I–A.IV

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