Clinical features and outcome in a Danish cohort of juvenile dermatomyositis patients

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Abstract

Objective

To assess disease characteristics and outcome in Danish juvenile dermatomyositis (JDM) patients (1977–2007).

Methods

Medical record review of hospital records identified from the National Patient Register.

Results

Fifty-seven JDM patients were identified. Follow-up time was 7 years (range 0.06–30). Female:male ratio was 2.5:1. Mean age at disease onset was 7 years (SD±3.7), range 1.5–16.0 years. Diagnostic delay was 0.7 years (SD±1.6), range 0.04–9 years. Mean disease duration was 3.7 years (SD±3.5), range 0.7–9 years. Thirty-nine patients (70%) were in full remission. Three patients (5%) were deceased.

Disease/treatment-induced damage was present in 35 (61%) patients. Decreased pulmonary function occurred early in the disease course (median 10 months), osteoporosis and calcinosis occurred later (median 18 and 22 months). Four patients developed persistent damage within the first 6 months, four developed calcinosis within the first year.

Shorter disease duration was associated with less damage ($p=0.004$). In a multivariate assessment analysis age >10 years at disease onset was associated with more damage ($p<0.01$), OR 10.96 (CI 1.6–73.6), and disease duration >4 years was associated with calcinosis ($p=0.01$) OR 23.2 (CI 2.6–206.2).

Conclusion

We present a nationwide retrospective study of Danish JDM patients from 1977–2007. Although 70% were in remission, 61% of the patients had clinical signs of damage. Only a few patients developed damage within the first year of the disease. Longer disease duration and higher age at disease onset was correlated with more disease damage.

Key words

Juvenile dermatomyositis, outcome assessments, Myositis Damage Index, calcinosis.

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Introduction

Juvenile dermatomyositis (JDM) is a rare autoimmune disease of unknown aetiology characterised by chronic inflammation primarily in the skeletal muscle and skin (1, 2). Due to more efficient treatment, prognosis has improved during recent decades. However, it is still a severe disease with a relatively high morbidity and mortality, and a high incidence of damage (2, 3).

Since 1975 the diagnosis of dermatomyositis (DM) has been based on the Peter and Bohan criteria (2, 4, 5), but revised criteria adding magnetic resonance imaging (MRI) as an important diagnostic tool have been proposed by the Paediatric Rheumatology European Society Working Group on JDM (6).

To achieve a more comprehensive description of the disease, The International Myositis and Clinical Studies group (IMACS) and Pediatric Rheumatology International Trials Organisation (PRINTO) have developed tools for measuring disease activity in myositis (7, 8), and a Myositis Damage Index (MDI) has been developed to describe JDM damage.

Epidemiological studies, mainly from North America, Ireland and the UK, have been described in the literature (9-12). This is the first published study describing a nationwide cohort from Denmark. Only a few studies have described the long-term outcome of JDM. In 2005 Huber and Feldman (3) reviewed the JDM-outcome-data for the past 4 decades; mortality and morbidity have decreased and most of the children with JDM recovered well, although some children continued to have disease activity or developed damage. Three recent long-term follow-up studies, using the MDI as a score tool found cumulative damage in 69–90% of the patients after up to 16.8 years of follow-up (13-15), thus suggesting that long-term damage is higher than previously expected.

The objective of this study was to describe the frequency, onset symptoms and damage of JDM diagnosed in Denmark 1977–2007, and to identify possible outcome predictors.

Material and methods

Patients were identified from the National Patient Register in Denmark (1977–2007), a register that enrols all hospitalised patients in the country. The register was searched for JDM, polymyositis, and related diagnoses *e.g.* overlap syndrome (ICD 8–10 diagnostic codes). Medical records were identified, and the results were obtained through medical record review by the principal investigator. In complicated cases a co-investigator was consulted in order to achieve agreement.

JDM was defined as dermatomyositis (DM) with onset before 16 years of age. Patients were classified as having *definite* or *probable* JDM according to the Peter and Bohan criteria (4, 5). Characteristics of *definite* dermatomyositis include a typical rash (heliotrope rash over the eyelids and Gottron´s papules over the digital extensor joint surfaces), plus three of four additional criteria: proximal symmetrical muscle weakness, increased serum levels of muscle enzymes, muscle biopsy consistent with myositis, and electromyography (EMG) showing myopathy and denervation. *Probable* JDM is defined as the typical rash and two of the four additional criteria.

The sensitivity and specificity of the Peter and Bohan criteria have not been validated in children with myopathies (1, 2), and we had the following methodological considerations:

– Only patients with an exact description of heliotrope eyelid rash or Gottron's papules were classified as having classic JDM skin rash. Other descriptions of skin rash or isolated periorbital oedema were classified as non-specific skin rash.
– In children EMG and muscle biopsy are rarely used, as they are painful invasive procedures. Often MRI replaces these procedures as a diagnostic tool even if there is no standardised method to evaluate MRI in JDM (1, 6). In the actual cohort, MRI has been used as a diagnostic tool since 2003. MRI-findings presenting muscular inflammatory abnormalities, depicted by MRI showing intramuscular oedema as high signal intensity on T2-weighted and short thau inversion recovery (STIR) MRI images, were regarded as a positive criterion for the diagnosis.

– A muscle biopsy described as consistent with myositis (perifascicular atrophy, perivascular inflammatory infiltrates, internal myonuclei and necrosis of muscular fibres) by the local pathologists were considered as a positive criterion for the JDM diagnosis.

Identification of the first definite JDM symptom, reported by the parents, was designated as the date of disease onset. The diagnostic date was defined as the day when a physician for the first time used the definition (juvenile) dermatomyositis.

Remission was defined as patients without biochemical or clinical evidence of disease activity for a minimum of 6 months and being without medical treatment.

The follow-up data was from the date of the last registered visit. If the patients were transferred from a paediatric to an adult department, medical reports were, if possible, obtained from the adult department as well.

Disease damage was defined as irreversible or persistent changes in anatomy, physiology or function, which existed for more than 6 months. The date of damage onset was defined as the day when a physician for the first time described the findings of damage. For the database we used the items employed in the Myositis Damage Index (MDI) and the MYODAM-VAS (7, 8). These score tools have recently been validated in a retrospective setting (14).

Approval was obtained from the local Ethics Committee, Copenhagen.

Statistics

Data are presented as median with range or with mean and SD as appropriate. Differences in distributions of non-paired independent variables were tested using chi-square or Fisher's exact test as appropriate.

Correlations were calculated using the non-parametric Spearman's test. To identify possible predictors of damage a binary logistic regression analysis was used. Level of significance was 5%. "SPSS" statistics software, version 15.0 was used for the statistical calculations.

Results

Of 137 registered patients, 112 had retrievable medical records and 25 could not be identified. Sixty-four patient records were classified as either JDM or polymyositis. Seven patients had polymyositis without dermal abnormalities and were not included in the calculations of this study due to inconsistent disease description, making it difficult to distinguish them from infectious myositis. Fifty-two patients were classified with definite JDM and 5 with probable JDM. Thus, 57 patients were included in the final analysis (41 females/16 males).

With an average of 1,077,481 children per year in Denmark in the 30-year follow-up period, the 57 patients represent an annual incidence of 1.8 per million children (range 0–3.6) with steady frequencies in the follow-up period.

The mean age at disease onset was 7 years (SD±3.7), ranging 1.5–16 years. The mean disease duration from onset till diagnosis was 8 months (SD±1.6), range 0.04–9 years.

Clinical symptoms at disease onset

The most frequent symptoms at disease onset were: proximal muscle weakness,

Table I. Clinical features at presentation (first 3 months), n=57.

Clinical feature	Patients with registered information in medical records	Patients with positive findings (%)
Proximal muscle weakness	55	53 (93)
Fatigue	52	47 (82)
Myalgia	51	43 (75)
Non specific skin rash	53	43 (75)
Gottron's papules	48	42 (74)
Heliotrope rash	49	38 (67)
Arthralgia	33	23 (40)
Periungual capillary changes	31	20 (35)
Weight loss	46	19 (33)
Fever	51	17 (30)
Vascular changes, incl. Raynaud's	33	16 (28)
Arthritis	46	15 (26)
Contractures	35	15 (26)
Lymphadenopathy	42	14 (25)
Gastrointestinal complaints	32	14 (25)
Dysphagia	38	13 (23)
Infection	47	10 (18)
Muscle atrophy	49	9 (16)
Skin ulceration	52	9 (16)
Dyspnoea	52	9 (16)
Dysphonia	31	6 (11)
Calcinosis	29	3 (5)
Lipodystrophy	10	2 (4)

Table II. Diagnostic investigations and percentage of abnormal findings in 57 patients with juvenile dermatomyositis.

Investigation	Number investigated (%)	Abnormal findings (%)	Findings Median U/l, (Min.-Max.)
Muscle biopsy	37 (65)	34 (92)	
Creatine kinase (CK)	54 (95)	33 (61)	1744 (30–19.100)
Lactic acid dehydrogenase (LDH)	44 (77)	42 (95)	1411 (139–17.324)
Alanine aminotransferase (ALT)	28 (49)	20 (41)	45 (11–417)
Aspartate aminotransferase (AST)	25 (44)	14 (32)	68 (13 – 3.290)
Aldolase	36 (63)	25 (69)	12 (4–44)
Electromyography (EMG)	23 (40)	18 (78)	
MRI scan	15 (26)	15 (100)	

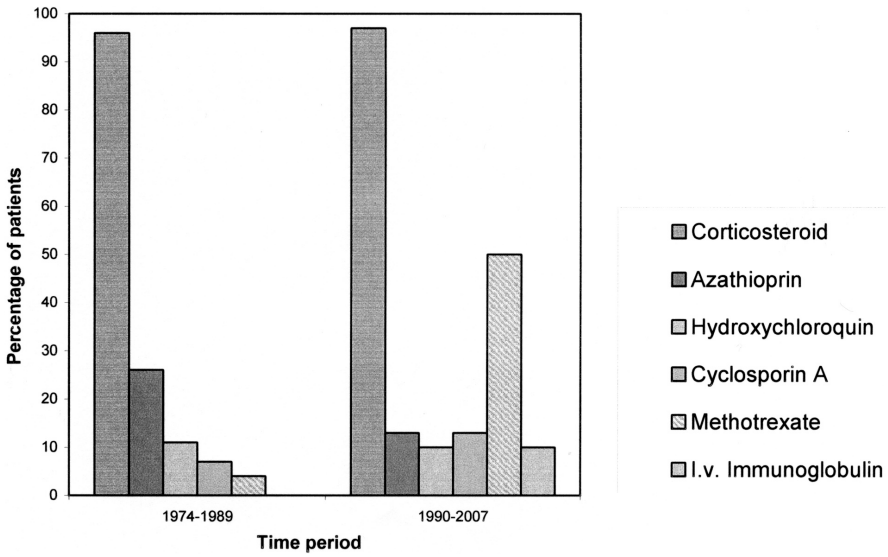

Fig. 1. Initial medical treatment used in two time periods.
1.7% received no drugs, 30% received 1 drug, 19% received 2 drugs, 25% received 3 drugs and 10% received 4 drugs or more. From 1990 all patients received additional immunosuppressant medicine in addition to prednisolone, and 65% received more than one additional immunosuppressant. From 1974–1990 only 50% received more than 1 drug.

Table III. Clinical damage registered in 57 JDM patients. Damage is registered if the patient had at least 1 period with the item lasting at least 6 months.

Organ system	Damage feature according to MDI*	Patients with feature present in the disease course (%)
Muscle	Muscular dysfunction: Decreased aerobic exercise capacity and/or muscular atrophy	23 (40)
	Muscle weakness not attributable to active disease	21 (37)
Cutaneous	Calcinosis	24 (42)
	Lipodystrophy	1 (2)
Skeletal	Joint contractures (limitation of motion)	19 (33)
	Osteoporotic fractures	8 (14)
Gastrointestinal (GI)	Dysphagia, GI dysfunction	0
	Infarction or resection of bowel	1 (2)
Pulmonary	Impaired pulmonary function	8 (14)
	Dysphonia	0
	Pulmonary fibrosis	1 (2)
Ocular	Cataract, visual loss	0
Infection	Chronic, Multiple	0
Malignancy		0
	Damage	35 (61)
	No damage	19 (33)
	Death	3 (5)

*MDI: Myositis Damage Index.
The following MDI features could not be assessed: Vascular necrosis, arthropathic deformity, alopecia, cutaneous scarring/atrophy, poikiloderma, steatosis, pulmonary hypertension, cardiovascular-, peripheral vascular- and endocrine damage.
Additionally the following MDI features had more than 50% missing values at last follow-up for those in remission: impaired pulmonary function, pulmonary fibrosis, dysphonia, calcinosis, lipodystrophy.

fatigue, Gottron's papules, non-specific skin rash, heliotrope eyelid rash, loss of muscle function, myalgia and arthralgia (Table II). Two patients did not have dermal changes at the time of diagnosis, but presented with a rash after 3 weeks and 14 months, respectively. Contractures at first medical visit were more frequent in the beginning of the period (1976–1980) whereas arthritis and vasculitis primarily was described in the patients after 2000. No other change in disease patterns at diagnosis was observed

Diagnostic investigations at disease onset

The diagnostic tests performed for each patient were rather inconsistent (Table II).

Serum creatine kinase was measured in most patients (95%). At disease onset high levels of muscle enzymes were seen in 49 patients (86%) of which 36 (63%) had elevated levels in two or more enzymes. Five patients had normal levels of muscle enzymes. No correlation was found between the level of elevated muscle enzymes at disease onset and disease outcome (p=0.55).

Muscle biopsy was performed in 37 patients with abnormal results in 34 (92%) patients.

MRI findings compatible with myositis were seen in all investigated patients. Elevated muscle enzymes or positive findings in biopsy and MRI did not predict disease outcome (overall damage, disease duration, calcinosis).

Medical treatment

The medical therapies were not standardised and the treatment varied according to disease severity, experience of the treating physician, and change in treatment practices throughout the 30-year follow-up period.

All but one patient received systemic corticosteroids as initial therapy. Additional immunosuppresants were used in 17 patients at disease onset. At last follow-up 46 of 57 had received other immunosuppressants, mainly methotrexate (n=26), in combination with corticosteroids. A change in treatment practice in the follow-up period were seen; since 1990 methotrexate was chosen as the most frequent drug added to corticosteroid therapy (Fig. 1) and all patients had received at least one immunosuppressant in addition to prednisolone, whereas, before 1990 additional immunosuppressants were reserved to patients not recovering on prednisolone alone.

In addition to medical treatment, all but two patients received physiotherapy. It was not possible to evaluate the quality of this treatment due to inconsistent data on this subject in the medical records.

Clinical status at the time of follow-up

At the time of follow-up 10 patients (18%) had active disease and 39 (68%) were in remission. Five patients' medical records were lost to follow-up. Three patients (5%) were deceased, all female, aged 5, 7 and 10 years. One died from an infectious disease of unknown ethiology, two from fulminant mucosal bleeding episodes (epistaxis and GI-ulcer). The deaths occurred 3, 18 and 22 months after disease onset.

The median follow-up time from disease onset to the last registered visit was 7 years (range 3 weeks – 29 years). Median time to remission was 3.7 years (range 7 months to 9 years); 6 (11%) patients had disease duration less than 2 years; 18 (32%) had a chronic disease course lasting more than 4 years, no patient had a cyclic course. Two patients developed JDM with overlap Mixed Connective Tissue Disease/scleroderma after 4 and 8 years.

Organ damage at the time of follow-up

Damage was present in 35 of 57 patients (61%). Nineteen patients (33%) had no damage. The most frequent types of organ damage were calcinosis, muscular dysfunction, joint contractures, impaired pulmonary function and osteoporosis (Table III).

One patient had pulmonary fibrosis at diagnosis (diagnostic delay 9 months). In general, decreased pulmonary function occurred early in the disease course (median 10 months), whereas osteoporosis and calcinosis occurred later (median 18 and 22 months, respectively) (Fig. 2). Only four patients developed signs of persistent damage within the first 6 months, and only four patients developed calcinosis within the first year.

Damage is normally defined as irreversible changes, but we observed that the MDI score in most patients (65%) decreased during the total follow-up period. The maximum cumulated MDI-score had a median of 2 (range 0–7) whereas the MDI-score decreased to a median of 0 (range 0–5) at the last visit.

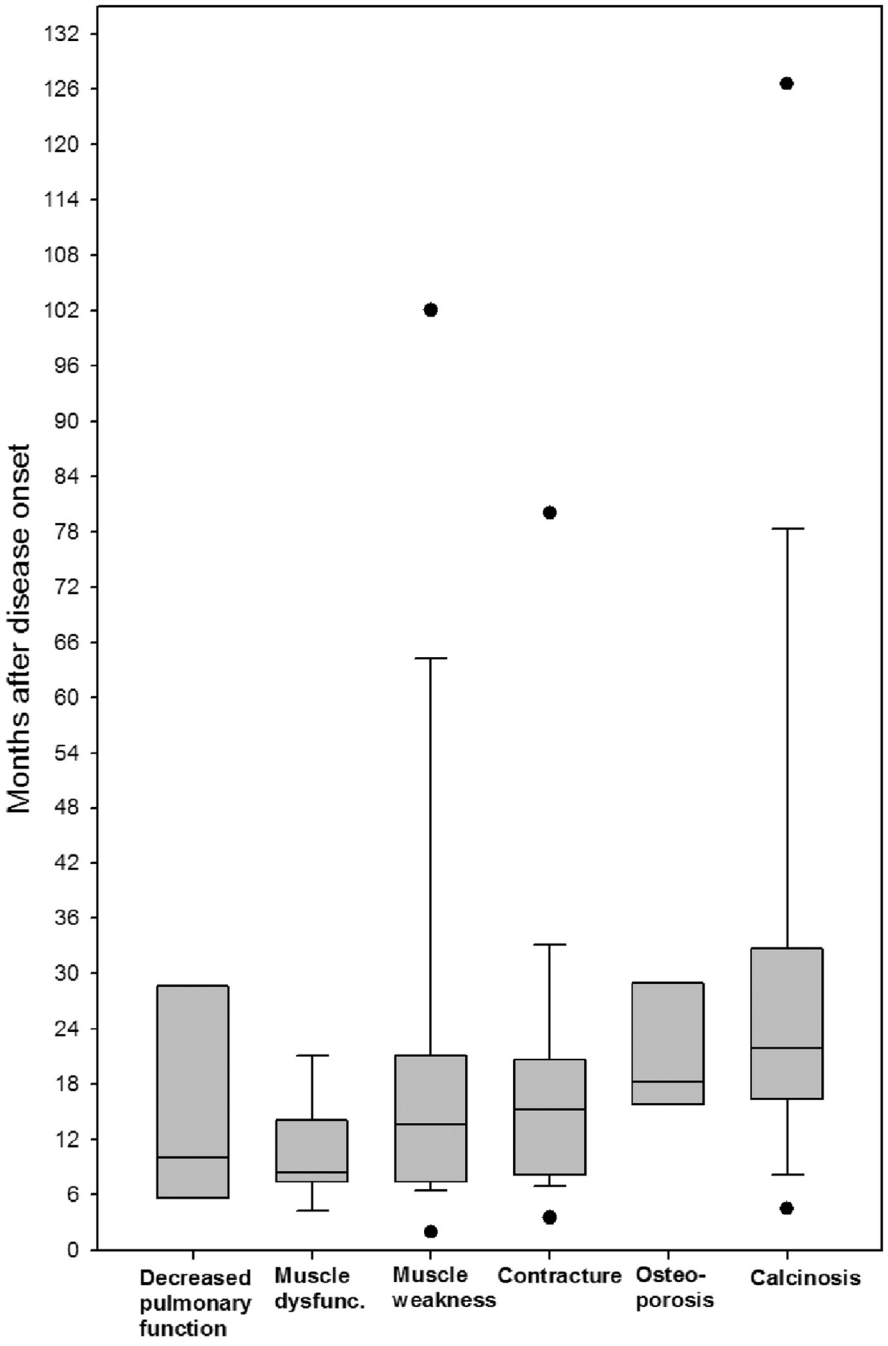

Fig. 2. Time of first registration of damage in 57 JDM patients. A box-and-whisker plot of time for the first registration of damage in 57 patients with juvenile dermatomyositis. Median and interquartile ranges are illustrated in the figure.

There were no significant differences in outcome for patients treated before and after 1990 (Table IV). However, the median time to remission in the period 1977–1989 was 48.2 months (range 17.1–214.9 months) whereas it was 41.5 months (range 9–32.1 months) in the period 1990-2007, thus, though not significant (p=0.683) a trend towards shorter disease duration was seen in the last period.

We tested for correlations between age, gender, diagnostic delay, time for initial treatment, clinical symptoms, muscle enzymes, medication used, disease duration and damage. Short disease du-

Table IV. Disease outcome in 34 JDM patients, all in remission.

Outcome	n (%)	Number of patients 1975–1989 n (%)	Number of patients 1990–2007 n (%)	*p*-value
Total number of patients	34	18	16	–
Overall damage	19 (56)	10 (56)	9 (50)	1.00
- Calcinose	14 (41)	5 (28)	9 (50)	1.00
- Moderate/severe decreased muscle function	4 (12)	3 (17)	1 (6)	0.16
- Osteoporosis	4 (12)	2 (11)	2 (11)	1.00
- Pulmonary	4 (12)	2 (11)	2 (11)	1.00
- Contractures	6 (18)	5 (28)	1 (6)	0.18
No damage	15 (44)	8 (44)	7 (39)	1.00
Death	3 (9)	2 (11)	1 (6)	1.00
Remission in less than 2 years	11 (32)	5 (28)	6 (33)	0.72

No significant outcome was demonstrated between the two time periods by chi-square/Fisher's exact *t*-test.

Table V. The rate and odds ratios with 95% confidence intervals of achieving damage/calcinosis within categories of risk factors. Best-fitting model for predictors of damage and calcinosis obtained by binary logistic regression.

Damage risk		N	n	%	*p*-value	OR	95%CI
Age at disease onset	0–4.5 years	17	8	47.1	–	Ref.	–
	4.6–10 years	19	12	63.2	0.33	2.11	0.47–9.48
	>10 years	16	14	87.5	**0.01**	**10.96**	1.63–73.58
Diagnostic delay	0–6 months	26	14	53.8	–	Ref.	–
	>6 month	26	20	76.9	0.24	1.4	0.79–2.61
Disease duration	0–2 years	15	8	53.3	–	Ref.	–
	2–4 years	13	8	61.5	0.87	1.2	0.21–6.4
	>4 years	24	18	75	0.32	2.1	0.48–9.54
Gender	Male	15	9	60	0.25	0.4	–
	Female	37	25	67.6	–	Ref.	0.09–1.9
Diagnostic year	1974–1989	21	13	61.9	–	Ref.	–
	1990–2007	31	21	67.7	0.48	1.6	0.41–6.6
Calcinosis risk		*N*	n	%	*p*-value	OR	95%CI
Age at disease onset	0–4.5 years	17	8	47.1	–	Ref.	–
	4.6–10 years	19	8	42.1	0.82	0.8	0.11–5.6
	>10 years	16	7	43.8	0.72	0.7	0.09–5.16
Diagnostic delay	0–6 months	26	9	34.6	–	Ref.	–
	>6 month	26	16	61.5	0.94	0.92	0.11–7.9
Disease duration	0–2 years	15	3	20.0	–	Ref.	–
	2–4 years	13	3	23.1	0.98	0.97	0.13–7.24
	>4 years	24	17	70.8	**0.01**	**23.15**	2.6–206.18
Gender	Male	15	6	40.0	0.21	0.29	0.04–1.99
	Female	37	16	45.9	–	Ref.	–
Diagnostic year	1974–1989	21	7	33.3	–	Ref.	–
	1990–2007	31	16	51.7	0.27	2.52	0.48–13.26

N: Total number of patients in category; n: number of patients with feature present; OR: odds ratio; CI: confidence interval.

ration was associated with less damage (p=0.004). No other correlations were identified.

In a multivariate analysis (binary logistic regression) (Table V) it was found that age >10 at disease onset had a significantly increased risk of achieving damage (p<0.01), OR 10.96 (CI 1.6–73.6), and that patients with disease duration >4 years had increased risk of developing calcinosis (p<0.01), OR 23.2 (CI 2.6-206.2).

Discussion

This is the first long-term retrospective follow-up study characterising a nationwide Danish cohort of JDM patients in a 30-year period. A significant proportion of the patients had clinical signs of damage increasing with the duration of disease. We did not find any markers of disease activity predicting the disease outcome, but a disease onset at late age (>10 years) was associated with increased damage, and disease duration of more than 4 years was associated with increased calcinosis.

In our study, few patients developed damage within the first year of the disease and longer disease duration was associated with more damage. Likewise, a recent study from the IMACS group describes duration of active disease as a risk factor for myositis damage (14), and the study of Ravelli *et al*. (13) finds a chronic disease course to be the strongest predictor of poor prognosis. The IMACS study (14) and a newly published study, describing the Norwegian JDM population (15) find that a high disease activity in the early disease course was associated with higher damage score at follow-up. These combined findings indicate that early diagnosis and treatment is of importance.

We observed a decrease in MDI-score over time in 65% of the patients, indicating that damage over a longer time period could in fact be reversible. However, with more than 50% missing values at last visit these results should be interpreted with care.

Our study also found that higher age at disease onset was associated with more damage, but we did not find any age related disease pattern at disease onset to explain this finding. An age dependent JDM disease pattern has previously been shown by Pachman *et al*. (16) who found that JDM often affects young children and is often preceded by a history of infection. This finding could not be confirmed in our study, which could be due to missing data.

Previously published incidence rates have ranged from 1.9–5 cases per million children/year (9-11). In our popu-

lation the incidence rate was 1.8 cases per million children/year. This suggests a relatively low incidence in the Danish population, but might reflect problems with the ascertainment rate, as 18% of the 137 charts could not be identified.

Disease characteristics in our cohort are comparable with other JDM register cohorts regarding male/female-ratio (9, 13, 15), age of diagnosis (9, 13,15), disease duration (13, 15), damage (3, 14, 13, 15) and mortality (2, 11, 15).

The exact time of disease onset was often difficult to define, however, the average time of 8 months from disease onset till diagnosis is comparable to other studies (9, 12, 15). Skin rash was observed in most children at disease onset, but several children were initially incorrectly diagnosed as having more common skin symptoms, *i.e.* eczema, allergic rash/oedema or non-specific viral rash indicating underestimation – or delay – of the diagnosis if the physician was not aware of the condition.

Most symptoms at disease onset were comparable to those in other studies (9, 12, 15). Arthritis was seen in 37% of the patients, corresponding with incidence rates from 23–43% in recent publications (12, 15), but less than described in a large follow-up by Tse *et al*. (18) showing an incidence of 61%.

Disease- or corticosteroid-induced damage was frequent (61%) and was correlated with longer disease duration. It could be speculated, whether there is coherence between the changes in medical practice concurrently with the shorter disease duration in the same period, as the disease duration has slightly decreased from 48.2 months before 1990 to 41.5 months after 1990, but no significant difference was discovered. A type 2-error could not be ruled out on this point because of the relatively low number of patients included. Furthermore, as treatment was not standardised there may be a bias towards treating the most severely affected patients with additional immunosuppressive drugs, illustrating the difficulties in estimating the effect of medical treatment in retrospective investigations.

Calcinosis was present in 42% of the patients, corresponding with incidences from 13–60% in other studies (9, 13, 14). It has been argued that early treatment with corticosteroids in addition to methotrexate reduces the risk of developing calcinosis (17). This could not be shown in our study. Most calcinosis occurred more than 1 year after disease onset, and there was no correlation to medical treatment.

Osteoporotic fractures were present in 11% of the patients. Fisler *et al*. describes stress fractures in 14% (17). As only a few patients were diagnosed with a dual-energy x-ray absorbtiometry (DXA) scan (19%), further information on osteoporosis could not be achieved.

Eight patients (14%) had pulmonary fibrosis and/or impaired lung function which is significantly lower than previously reported (19, 20). Relatively few patients had diagnostic pulmonary investigations (18%), including pulmonary function tests and CT-thorax, and consequently, pulmonary symptoms may have been under-diagnosed.

Our study was subject to the classic limitations of retrospective data from disease registries and hospital records: many of the cases reported to the national register were not truly JDM, only positive clinical findings were described and there was a large variation in the amount of available clinical information. The number of JDM cases is probably underestimated as the estimate is biased downward when data is missing. Furthermore, it could be difficult to judge whether the diagnosis was correct, because the description of the items of the classification criteria, especially skin rash and the muscle biopsies, were incomprehensive in the medical records.

The use of the MDI and MYODAM-VAS has recently been validated (14), but these tools had certain limitations in our study. The MYODAM-VAS proved not to be useful in this retrospective setting as it includes a clinical judgement by the physician at bedside, whereas the MDI was quite beneficial even though the many missing data could provide an inaccurate description of the severity of damage. Damage is probably underestimated in the study, especially mild damage, as it will tend to be overlooked by physicians not trained in paediatric rheumatology.

A more comprehensive description of JDM course and damage needs to be tested in a clinical follow-up study. Furthermore, it will be of interest to explore the cumulated damage using the MDI as a scoring tool and to investigate whether some damage is reversible and disappears after a longer time of follow-up.

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