Outcomes and prognostic factors in Juvenile Dermatomyositis

Doctoral thesis by

Helga Sanner

Department of Rheumatology, Oslo University Hospital, Rikshospitalet

Faculty of Medicine

University of Oslo

2010

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo
No. 1064

ISBN 978-82-8072-549-3

Cover: Inger Sandved Anfinsen.
Printed in Norway: AIT Oslo AS.

Produced in co-operation with Unipub.
The thesis is produced by Unipub merely in connection with the
thesis defence. Kindly direct all inquiries regarding the thesis to the copyright
holder or the unit which grants the doctorate.

Acknowledgements

Most of this work was carried out at the Department of Rheumatology, Oslo University Hospital (OUH) from 2005-2009, while working as a research fellow / lecturer financed by the University of Oslo. I feel privileged to be given the opportunity to immerse myself in such a unique material. I am grateful to all JDM patients, control persons and their parents, for their willingness to participate in this study. This project has been a long journey, which would not have been possible without the support from many persons, mainly at OUH. I want to thank:

My main supervisor Berit Flatø for her active involvement in all phases of this work, from the idea through data collection, statistics and writing phase; her high scientific standards and throughout knowledge of pediatric rheumatology have been most inspiring and helpful.

My co supervisor, Jan Tore Gran (Head of Department in this period) for the idea behind the project, for institutional support and his extensive knowledge of rheumatology, for valuable contributions, and for having confidence in me.

Nurse Anita Tollisen for collecting and interpreting data about self-reported health. Anita has also written her Master`s degree on this material. Without Anita, practical handling of the patients would have been impossible. Nurse Hanne Ødegaard is also thanked for valuable practical help.

Mona Røisland, physiotherapist and coordinator of the National Resource center of Pediatric Rheumatology, for carrying out muscle strength testing (CMAS) in most patients and controls. Her flexibility in doing so has been most valuable.

Bjørn Johansen (Department of Respiratory medicine), for help with pulmonary function tests, and for patiently sharing his extensive knowledge in respiratory physiology with me (giving me a piece of understanding). Also Wenke Lunde and the staff at the same department for the flexibility in performing the pulmonary function tests.

Radiologists Eva Kirkhus and Else Merckoll for scoring and interpreting MRI data and Trond Mogens Aaløkken for scoring and interpreting HRCT data; to all the three for valuable discussions and contributions.

Researcher Benedicte Lie and senior consultant Eli Taraldsrud at the Institute for immunology, for important contributions and knowledge on HLA genes and autoantibodies, topics I find rather challenging.

Consultant Thorild Garen, for valuable help with scanning and handling of data; her qualifications were most important in the early phase of the project, in a period when data handling was new to me.

Statistician Are Hugo Pripp at the institute of Biostatistics for valuable input and discussions about statistical analyses.

Also, pediatricians Ellen Nordal from University Hospital of Northern Norway and Marite Rygh from St Olav hospital are thanked for help with recruiting patients from the middle and northern parts of Norway.

Parts of the study were financed by the research fond at Department of Rheumatology at OUH, the National Resource center of Pediatric Rheumatology as well as Olga Immerslund foundation.

At last, my dear husband, scientist and co author Ivar is thanked for discussions and contributions in all phases of this project, for his love and support, for believing in me, and for never stop challenging me.
Our children Snorre, Marie, Øyvind and Einar for help testing out the information sheets for the juvenile patients and controls, and more importantly, for always remaining me what really matters in life, also in the periods I had to bury myself in the “doktorgraven”.

☺

Table of contents:

1. List of papers

Paper I

Cumulative organ damage and prognostic factors in juvenile dermatomyositis: a cross-sectional study median 16.8 years after symptom onset.
Sanner H, Gran JT, Sjaastad I, Flatø B.
Rheumatology; 2009 48(12).

Paper II

Long term muscular outcome, predisposing and prognostic factors in juvenile dermatomyositis: - a case control study.
Sanner H, Kirkhus E, Merckoll E, Tollisen A, Røisland M, Lie BA, Taraldsrud E, Gran JT, Flatø B.
Arthritis Care Res; published online 2010 Mar 30

Paper III

Pulmonary outcome in juvenile dermatomyositis: a case control study.
Sanner H, Aaløkken TM, Gran JT, Sjaastad I, Johansen B, Flatø B.
Submitted.

2. Abbreviations

JDM	juvenile dermatomyositis
OUH	Oslo University Hospital
OSR	Oslo Sanitetsforenings Revmatismesykehus
IIM	idiopathic inflammatory myopathies
DM	dermatomyositis
PM	polymyositis
MRI	magnetic resonance imaging
MSAs	myositis specific antibodies
CK	creatine kinase
LD	lactate dehydrogenase
ASAT	aspartate aminotransferase|
HLA	human leukocyte region
TNF	tumor necrosis factor
MAAs	myositis associated antibodies
ANA	anti nuclear antibodies
RCT	randomized controlled trials
MMT	manual muscle test
SF-36	short form 36
IMACS	International Myositis Assessment & Clinical Studies Group
PRINTO	Pediatric Rheumatology International Trials Organization
HAQ /Child-HAQ	Health assessment questionnaire / childhood health assessment questionnaire
MDI	myositis damage index
CMAS	Child Myositis Assessment Scale
ILD	interstitial lung disease
DLCO	diffusion capacity of carbon monoxide
TLC	total lung capacity
HRCT	high resolution computed tomography
MDAA	myositis disease activity assessment tool
DAS	disease activity score (for JDM)
VAS	visual analog scale
CHQ	Child Health Questionnaire
PFT	pulmonary function tests

3. Introduction

Juvenile Dermatomyositis (JDM) is a very rare, presumably autoimmune disease of childhood characterized by proximal muscle weakness and a classical rash. Being a systemic vasculopathic disease, other organs like the lungs, heart and gastrointestinal tract can also be affected (1).

Before 1960, there was no effective treatment for JDM. A review from 1964 introduced the "rule of thirds" for untreated JDM (2), 1/3 of the patients died, 1/3 evolved serious functional disability and 1/3 recovered. After first corticosteroids and gradually other immunosuppressive agents were introduced in the treatment from the early 1960th, the mortality rate decreased to < 5 % in the new millennium. However, even though the survival rate is increasing, many patients still develop calcinosis and other complications. Thus, there has been an increasing interest in long-term outcome of JDM (3).

At the time our study was initiated, data on long-term outcome was scarce, and we therefore had no good answer to the question frequently asked by the parents of JDM patents: "What is the prognosis of my child?" Working a period as a clinician at the Department of Pediatric Rheumatology at Oslo University Hospital (OUH), I developed an interest for this disease. Even though being extremely rare, it is said about JDM: "if you have ever seen a patient, you never forget" and "the clinical manifestations in JDM are some of the most interesting in all pediatric medicine" (4). The few patients I saw during this period, I certainly did not forget, and I developed and eager to find some answers to this important question.

During the 1990th, tools for measuring myositis outcomes had been developed by two international collaborations, making it possible to measure outcomes utilizing standardized methods. This is an important basis for the possibility of comparing myositis studies addressing outcomes.

In Norway, most JDM patients have been treated at the department of Rheumatology, OUH (before 2000 being Oslo Sanitetsforenings Revmatisme-sykehus, OSR) or at the pediatric departments of the other major hospitals in Norway. Also, thanks to the Norwegian population register, we have unique

opportunities to trace former patients who are no longer in the hospital system, being an important premise for this doctoral thesis.

4. Background

Idiopathic inflammatory myopathies

JDM belongs to the idiopathic inflammatory myopathies (IIM), being chronic immune mediated muscle diseases. Adult onset IIM can be classified in several clinicopathologic subsets. The same subsets can be applied in juvenile IIM, but the frequency distribution for the various subsets differ between juvenile and adult onset disease (5). These subsets are as follows (modified from Rider) (5):

- Dermatomyositis (DM)
- Polymyositis (PM)
- Overlap myositis
- Inclusion- body myositis
- Amyopathic dermatomyositis
- Other types (e.g. cancer associated myositis, orbital myositis, granulomatous myositis, eosinophilic myositis etc).

Unlike in adults, DM is the far most common type of juvenile IIM, representing 85-95% of the cases (6). The age limit for juvenile vs. adult onset DM is not clearly defined; 16-20 years have been used in different studies, although 18 years seems to me most common (5). Juvenile PM (which lacks the classical rash) is much rarer, and constitutes ~8% of juvenile IIM cases (7) and over lap myositis (myositis associated with other autoimmune diseases) ~7% (8;9). Amyopathic dermatomyositis is rare in children (1). The other forms listed above, are extremely rare or absent in the pediatric population.

Diagnostic criteria for dermatomyositis and polymyositis

In 1975, Bohan and Peter developed diagnostic criteria for dermatomyositis and polymyositis (10;11)(table 1). The Bohan and Peter criteria are the preferred criteria used for diagnostic work-up in JDM. They are also widely applied in research, and are recommended used as inclusion criteria for enrollment of adult and juvenile PM and DM patients into clinical trials (12). However, the specificity and sensitivity of

these criteria have never been tested in the juvenile population (13). Many investigators think the criteria are outdated in pediatric practice, since performance of muscle biopsies and electromyography often is avoided in classical JDM cases (14). Being more that 30 years old; these criteria do not include advantages in diagnostic procedures like magnetic resonance imaging (MRI) of muscles or myositis specific autoantibodies (MSAs). Also, the degree of abnormality required for each criterion is not specified (e.g. muscle enzymes). Several attempts have been made in order to develop new classification and diagnostic criteria for inflammatory myopathies (14-16), but none of these are internationally accepted. However, an international effort to develop new classification criteria for IIM is now under way (17;18).

Table 1. Bohan and Peter Criteria (adapted from Bohan and Peter) (10;11)

1. Characteristic cutaneous changes (e.g. heliotrope, Gottron)
2. Symmetric, often progressive weakness of proximal musculature
3. Elevation of the serum level of one or more of the muscle enzymes, creatine Kinase (CK), lactate dehydrogenase (LD), aspartate aminotransferase (ASAT) or aldolase
4. Electromyographic (EMG) changes characteristics of myopathy and denervation
5. Muscle biopsy documenting histological evidence of perifascicular atrophy, perisvascular inflammatory infiltrates and necrosis of muscle fibers

Definite DM requires the skin criterion (criterion 1) and 3 of the muscle criteria (criteria 2-5); whereas *probable DM* requires the skin criterion and 2 muscle criteria.
Exclusion criteria: The diagnosis of PM/DM requires that all other forms of myopathy (e.g. infectious, metabolic, endocrine disorders and dystrophic myopathies) are excluded by appropriate clinical, laboratory, genetic or pathologic techniques.

By consensus, a probable or definite adult or juvenile DM is recommended for inclusion in clinical trials (12).

Epidemiology

JDM is a very rare disease; the most reliable data for annual incidence (1.9 - 3.2 per million children) is reported from population based studies in UK and USA (19;20) (table 2). Data from Scandinavian countries is limited by inclusion of only 4-13 cases (21-23). There is no reliable data for prevalence. A female predominance has been reported from the Western world (60-83% females) (table 2), but has not been found in studies from Japan and Saudi Arabia (40-42% females) (24;25). Some reports suggest that the female dominance is lower in younger age groups (26). The average age at onset is 7 years (13;19). In a recent study, 25% of JDM patients were < 5 years of age at disease onset (27). Even though an overrepresentation of black children has been reported from the UK (28), this was not found in USA (20), were the annual incidence estimates were comparable for whites and blacks (3.4 and 3.3 per million children), but slightly lower in Hispanics (2.7 per million children) (20).

Table 2: Juvenile IIM epidemiological studies*

	Oddis (29)	**Symmons (19)**	**Mendez (20)**	**Fujikawa (30)**
Year	1963-1982	1992-1993	1995-1998	1997
Country	USA	United Kingdom	USA	Japan
Source	Hospital based	Practitioners based	2 US national registers	Hospital based
Cases included	21 JDM	47 JDM	276 JDM	320 IIM
Age limit, years	<15	< 16	2-17	
Incidence/mill (95 % CI)	2.5	1.9 (1.4-2.6)	3.2 (2.9-3.4)	1.6
Female %		83%	70%	

*Only studies with at least 20 JIIM cases are included

Pathogenesis

The etiology of JDM is relatively unknown. A working hypothesis is that in genetically susceptible individuals, environmental factors may trigger immune dysfunction and specific tissue response in small vessel endothelium (in skin, muscle and other organs)(31).

The strongest genetic associations for autoimmune diseases, including JDM, are with genes in the human leukocyte region (HLA) in the major histocompatibility complex on chromosome 6 (7). In this region, multiple genes coding for proteins central to the immune system are clustered (including HLA class I, II and III molecules)(32). Alleles at the 8.1 ancestral haplotype (HLA-B*08-DRB1*0301-DQA1*0501), has been described as a strong immunogenetic predisposing factor for many autoimmune diseases in Caucasians, including adult DM and JDM (32-35). In JDM, an additional risk factor (DQA1*0301 allele) and several protective factors have been identified (36). However, HLA-DRB1 allele carriage frequencies have not previously been described in Scandinavian JDM patients.

Several other polymorphic loci have been associated with severe disease. Tumor necrosis factor alpha (TNF-α) 308A polymorphism has been associated to calcinosis, ulcerations and disease chronicity (37), and also small vessel occlusion (38). An Interleukin-1 polymorphism confers additional risk for development of calcinosis (39).

In two studies, most children had symptoms consistent with infection 3 months before onset of symptoms, suggesting an infectious trigger (27;40). Also geographical or seasonal clustering within the onset of the disease suggests environmental triggers. However, no specific infectious agents have been found in case control studies (41). Also, there are reports of JDM onset after vaccines, drugs and UV light exposure (31).

JDM is thought to be a *vasculopathic* condition (42). The small vessel endothelium (capillaries, venules and small arteries) in muscles, skin and other organs are important targets for the immune response (which involves humoral, cellular and innate immunity, and will not be further discussed) (1). The result of this process is swelling of the endothelium, causing necrosis, capillary thrombosis and thus obliteration of the lumen, which may lead to ischemia. This immune mediated endotheliopathy (or *vasculopathy)*, is thought to be more common than true

vasculitis. These changes can be studied in the nailfold region (enlarged loops, with capillary drop outs) and probably reflect what may be occurring in small caliber vessels in other organs. In the skin, these changes lead to variety of rashes, and in the gastrointestinal tract may cause pain, infarction and perforation (1;31;43).

In *muscle biopsies*, this endothelium swelling and obliteration of the lumen can be observed. The vasculopathy is thought to be the reason for the typical peripheral fascicular atrophy often seen. In more severe cases, muscle cell necrosis may occur, with minimal or no inflammation (inflammation most often seen in the perimysium and perisvascular) , probably because of an ischemic myopathy rather than immune attack on muscle cells (43).

The calcification in JDM is *dystrophic* (at sites of injured tissue with normal serum calcium and phosphorus levels)(44), and is found in muscles severely affected. Increased level of TNF-α has been associated with calcinosis (TNF-α 308A polymorphism). It is therefore believed that underlying inflammation might contribute to development of calcinosis (37), whereas calcium deposition previously was thought to be part of the scarring process (45).

Autoantibodies

Autoantibodies in IIM can be divided into *myositis-specific antibodies* (MSA), which are relatively specific to IIM, and myositis-*associated antibodies* (MAA), which are also seen in over lap syndromes or other autoimmune diseases. The MSA includes the antisynthetase antibodies (anti Jo-1 being most common), anti SRP and anti Mi-2, whereas examples of MAA are anti-Ku, anti-PMScl and anti-Ro (31). In adult DM and PM, MSAs are seen in almost 50% of the patients (46;47). At the time our study was initiated, MSA had been found in 4-11% of juvenile IIM patients, most commonly Mi2, but also SRP and anti-Jo1 had been described (5;48). MSA and MAA are associated with specific clinical features (e.g. antisynthetase antibodies and interstitial lung disease), immunogenetics and prognosis (35). Also, anti nuclear antibodies (ANA) with uncertain specificity had been found in up to 70% of JDM patients (49).

Clinical manifestations, disease course and treatment

The most common symptoms in JDM are progressive proximal and axial *muscle weakness* in addition to a classical, often pathognomonic rash (heliotrope rash,

Gottron's papules). Other frequent skin involvement includes periungual and malar erythema, and less commonly skin ulcers. Other symptoms are variable. Constitutional symptoms (fever, lethargy) can be seen early in disease course. Other organs as the joints (arthralgia, arthritis, contractures), lungs (dyspnoea, interstitial lung disease), heart (pericarditis, myocarditis), and gastrointestinal tract (dysphagia, bleeding, perforation), can also be affected (1). Lipodystrophy, being fat loss associated with metabolic alterations, is seen in 10-40% (50). As opposed to in adult onset IIM, malignant disease is very rare in JDM and equals the incidence in the general pediatric population(51).

A hallmark of JDM is *calcinosis*, which is described in 10-50% of patients (9;45;52;53), most often 1-3 years after diagnosis (range 0-20 years) (45;52). Four different patterns have been recognized: 1) cutaneous or subcutaneous plaques or nodules, 2) deposits that extend to muscles 3) along facial planes and 4) widespread calcium exoskeleton (54). Dependent on distribution, calcinosis may induce contractures (if crossing joint margins), pain due to nerve entrapment, ulcerations or inflammatory reactions during active deposition, or be infected (45;55). Calcinosis is known to be associated with functional disability (52).

JDM disease course is heterogenic; 3 distinctive disease courses have been recognized (52;56)

- *Monocyclic course:* permanent remission within 2-3 years (25-37%)
- *Polycyclic course:* periods of remission followed by relapse (11-27%)
- *Chronic, continues course*: persistent disease for longer than 2-3 years (44-52%)

Various studies have reported on disease course, but it should be noted that the definitions have varied (45;57); and is complicated by the lack of an established definition for remission. Some authors also use the terms unicyclic and non-unicyclic (37;58).

The aims of medical treatment are to control disease activity, prevent mortality and reduce long-term disability and complications. Since there are no randomized controlled trials (RCT) available, regimes are based on clinical

experience, uncontrolled retrospective reports and open- label prospective case series (5;59). First line treatment has since early 1960th been high-dose, oral corticosteroid therapy (1-2 mg/kg). In many centers, iv methylprednisolone (10-30 mg/kg/pulse) and and/or methotrexate (0.4-1 mg/kg/week) are added as first line agents, due to data suggesting that such regimes may reduce complications and increase the chance of early remission (60) (even though these data are based on historical reference groups). Hydroxychloroquine is used, especially to control rashes. For patients who do not adequately respond to first line treatment, other adjunctive steroid-sparing immunosuppressive therapies may be added (e.g. cyclosporine, azathioprine, cyclophosphamide, intravenous immunoglobulin, anti-TNF agents and tacrolimus). Importantly, and contrary to what was previously believed, early physiotherapy seems to be safe, also in patients with active myositis. This is supported by a study using MRI scans before and after a moderate exercise program, indicating no evidence of increased muscle inflammation after exercise (61).

Outcome

Outcome assessment

In 2001, the World Health Organization provided a framework for measuring health and health related domains, the International Classification of Functioning, Disability and Health (62). Disability is an umbrella term for impaired body structure and function, limitations in the ability to perform activities in daily life, and restrictions in the ability to participate in society (63;64). When applied in myositis research, examples of measures of body function and structures are Manual Muscle test (MMT) and MRI findings, whereas an example of a measure of limitation of daily activities and restrictions to participate in society is the short form 36 (SF-36)(64).

Given the poor prognosis for untreated JDM, studies published prior to the 1960th, focused primarily on mortality, considerable disability and to a lesser extent on complications like calcinosis. With more children surviving the disease, the focus of interest shifted from survival towards long-term morbidity like calcinosis, and functional outcomes (3;65). However, myositis outcome research has been limited by the lack of established outcome measures. An international effort defining such measures has recently been carried out by two international collaborative organizations. The International Myositis Assessment & Clinical Studies Group (IMACS) and the Pediatric Rheumatology International Trials Organization (PRINTO) have, by different processes, defined 3 important domains for assessment in therapeutic trials and natural history clinical research (66;67). These domains are: *disease activity* (potentially reversible with treatment), *disease damage* (irreversible changes in anatomy, physiology or function) and *health related quality of life*. The proposed core sets for these domains, are presented under Methods section page 27 (table 4).

Outcome studies

At the time our study was initiated, quality data on long term outcome was limited (3). It was known that the outcome had improved considerable since the “rule of thirds” for untreated JDM was introduced (1/3 died, 1/3 evolved severe functional impairment and 1/3 recovered) (2). Since the introduction of corticosteroid therapy in the 1960th, the mortality rate decreased from 9% in the early 1980s (3), and in 2000-2004 reported to be 0-6 % (table 3). However, as shown in table 3, most of these

studies are retrospective and include few patients. Some of them also include patients being followed for less than 2 years (patients early in disease course) and these studies have the lowest reported frequency of calcinosis (68;69). Some studies refer to disease course or remission, but the definitions of these terms vary, and make the results hard to compare. None of the studies have measured disease activity at follow-up by validated tools. Also, data on muscle weakness and functional disability are hard to compare, due to lack of standardized measures. Only two small studies have included follow-up examination (70;71).

Table 3. JDM outcome studies published before 2005*

	n	Methods	Follow-up yrs (range)	Death	Functional disability	Disease course	Weakness / rash	Calcinosis
Bitnum (2) 1964	168	Review of published cases		34%	33% ("crippled")			
Pachman (72) 1980	21	Prospective	Mean 4 (0.5-11)	0.5%	10%			43%
Chalmers (70) 1982	17	Follow-up examination	Mean 18.5 (8-36)		12%		35% / 41%	41%
Bowyer (45) 1983	47	Retrospective	Mean 5.5 (2-16)	2.1%	38%	Monophasic: 23%		51%
Miller (57) 1987	39	Retrospective + questionnaires	Mean 9 (3-22)	26%	12% (of survivors)	Mild: 15%	13% / -	30%
Collison (71) 1998	12	Follow-up examination*	10 (2-29)		25%		67% / 78%	
Ng (73) 1998	33	Retrospect + questionnaires	Mean 6.2 (2-18)	0		Monocyclic 42%		15%
Tabarki (74) 1998	36	Retrospective	Mean 4.9 (2-13)		22%	Monophasic 39%		42%
Shehata (24) 1999	25	Retrospective	Mean 4.5 0.5-9	0			48% / -	40%
Huber (52) 2000	65	Questionnaires + telephone interview	Med 7.2 (3-14)	1.2%	28% (child HAQ>0)	Monocyclic 37%	23% / 40%	34%
Sallum (68) 2002	35	Prospective + retrospective	Mean 3.5 (1-11) †	6%		Remission 59%	- /11%	14%
Singh (69) 2004	33	Retrospective	Mean 4.2 (0.6-13) ‡	6%		Monocyclic 73%	21% / 15%	27%

*Only studies with mean/median (med) follow-up time at least 3 years are included; all studies are hospital based. †15% followed ≤ 2 years, ‡ 30% followed ≤ 2 years.

In 2000, the result from a Canadian multi-center inception cohort was published (52)(table 3). Out of 80 identified patients, 65 (81%) could be contacted;

patients were interviewed by telephone or in person, and completed the Childhood Health Assessment Questionnaire (child HAQ). Calcinosis was found in 34%, 35% were still on immunosuppressive medication, but 72% had no physical disability measured by child HAQ. This study, although limited by lack of follow-up examination, represented a step forward in describing JDM outcomes.

Organ damage

Since many organs potentially can be involved in the IIM, a global, comprehensive tool for measuring damage in 11 organs and systems, the myositis damage index (MDI) (66;75) was developed by IMACS in the 1990th, using the pattern of the SLICC/ACR damage index for systemic lupus erythematosus (76). Damage is defined as persistent or permanent changes in anatomy, physiology, and function, being a result of previous active disease, complications of therapy or comorbid conditions (66). When our study was initiated, the MDI was still under validation, and no data on organ damage applying the MDI tool in a JDM cohort was available.

Muscular outcome

JDM causes inflammation in skeletal muscles (disease activity) which may lead to muscle scarring and atrophy (disease damage). Since these processes affect muscle strength and endurance, impairments of these are important outcome measures in IIM (1;64;77) and are included in both disease activity and damage domains (67;75). The manual muscle test (MMT) measures peak muscular force and is the most commonly used primary outcome measure in IIM therapeutic trials (66). There are different versions of MMT available, including 24 muscle subsets tested bilaterally and 8 muscle version tested unilateral (MMT-8), also both 0-5 and 0-10 grading scale have been used (12;78). At the start of our study, the MMT-8 version was recommended by IMACS for research purposes, since it compared with the 24 muscles version was less time consuming, and seemed to perform similar (78;79). The Child Myositis Assessment Scale (CMAS) is a performance- based instrument developed to evaluate muscle strength, endurance and physical function in juvenile IIM (80;81).

MRI of proximal thigh muscles is a method that can distinguish between muscular disease *activity* and *damage* (66). Short tau inversion recovery (STIR) or T2 weighted fat suppressed series are useful for detecting inflammation in muscle,

subcutaneous tissue and skin (increased water content) (82-84) whereas T1 weighted series assesses muscle fatty infiltration and atrophy and subcutaneous atrophy (84-86). Being a non-invasive test that visualize many muscle groups at a time, MRI is thought to have a role in detecting long term muscular complications of JDM (87). However, due to high costs and limited availability worldwide, MRI is not included in the core sets for disease activity or damage (66;67).

When our study was initiated, muscle weakness had been described in ~ 35% in two small studies which included follow-up examination (70;71), and *self-reported* muscle weakness (by patients or parents) in 23% of 65 patients (52)(table 3). However, no JDM outcome studies had utilized MMT or CMAS after long term follow-up. MRI detected fatty infiltration, atrophy and calcinosis/fibrosis had been reported in 3 small series, including 4-19 patients after 4-18 years of follow-up (71;86;88).

Pulmonary outcome

In adult polymyositis and dermatomyositis, pulmonary involvement, especially interstitial lung disease (ILD) is an established complication, resulting in high morbidity and mortality (89). The presence of antisynthetase antibodies is an important risk factor for ILD in IIM, and is seen in 30-40% of adult IIM patients vs. only 1-3% of JDM patients (90). However, serious and fatal lung involvement in JDM has been described in case reports (91;92). Restrictive ventilatory defects and reduced diffusion capacity of carbon monoxide (DLCO) have previously been described in two small JDM series (72;93). Also, calcinosis can be confined to the chest wall, and thus lead to restrictive ventilatory defects (94).

The preferred method for assessing restrictive ventilatory defects (small lung volumes) is body plethysmograph assessed total lung capacity (TLC). High resolution computed tomography, is a sensitive method to detect pulmonary disease, as ILD (95), and can also detect calcinosis in the chest wall. ILD confirmed by HRCT, has been described in a 5/10 patients with severe JDM (96). However, the prevalence of pulmonary function impairment and HRCT abnormalities in unselected JDM patients have never been investigated, and no controlled studies are available.

Prognostic factors for unfavorable outcomes

When our study was initiated, delay in treatment and inadequate treatment, had been recognized as risk factors for calcinosis and an unfavorable functional outcome (45;53;74). Also, a chronic disease course had been associated with physical disability (52), but no relation was found between severity at onset and outcomes. In most studies, patient characteristics like age at disease onset, gender and ethnicity, was not related to physical disability or calcinosis (45;72;97). On the other hand, Huber et al found that females had more physical disability (higher child HAQ scores) (52). Although rare in JDM, certain MSA (like anti-Jo1) are risk factor for severe disease (5). In a small longitudinal study of 12 JDM patients, ANA was associated with reduction in DLCO (93). Additionally, certain non HLA genes appear to be associated with a prolonged disease course (37).

5. Aims of the study

Main Aim

To investigate outcomes, predisposing factors, and early predictors of unfavorable outcomes in Juvenile Dermatomyositis patients, and explore how measures for disease activity and damage change from early disease stages through follow-up. Also we wanted to see how measures for muscular-, pulmonary- and health-outcomes in JDM patients differ from that of age- and sex-matched controls from the general population.

Specific aims

- To investigate the extent of organ damage (applying Myositis damage index) in Norwegian JDM patients after median 16.8 years (paper I).
- To explore how disease activity and disease damage change from first year post-diagnosis through follow-up (paper I).
- To compare muscle strength, physical health and pulmonary function in JDM patients with that in 1:1 age- and sex-matched controls from the general population (paper II-III)
- To investigate the extent of MRI detected muscular abnormalities and HRCT detected chest abnormalities in JDM patients (paper II-III).
- To identify early predictors (from the first year post-diagnosis) of organ damage, calcinosis and unfavorable muscular outcomes (paper II-II).
- To see how measures for cumulative organ damage, muscular and pulmonary outcomes, correlate with other disease measures at follow-up (paper I-III).
- To compare HLA-DRB1 allele carriage frequencies in JDM patients with that in healthy controls (paper II).

6. Study population and Methods

Study design

All papers in this thesis have a *cross-sectional* design (one follow-up examination of all patients). In order to identify predictors of the outcomes of interest (findings on the follow-up examination), a *retrospective* chart-review was done for all cases (with special focus on patient's characteristics and disease variables the first year post-diagnosis). In addition, for paper II and III, a *case - control design* (one age- and sex matched control per patient) was used.

Patients and controls

Patients

Inclusion criteria

1. JDM diagnosis in Norway between January 1970 and June 2006
2. Definite or probable diagnosis of dermatomyositis, according to the Bohan and Peter criteria
3. Onset of symptoms (muscle or skin symptom) before the 18th birthday
4. Minimum 24 months disease duration (from symptom onset) to the follow-up visit.
5. Age ≥ 6 years at follow-up (for paper II and III)

Exclusion criteria – none

Search strategies
Patients were identified from the following sources:

1. Department of Rheumatology, OUH.
   Our department is responsible for the care of children with rheumatic diseases in a region comprising 55% of the Norwegian population (2.6 million), and is also a referral centre for the remaining parts of the country.
   a) Manual search in the chart archive (1970-1980); this archive contains charts from OSR. - *17 patients identified*

b) Electronic search in the chart archive (1980→) *57 patients identified*
   - ICD- 8 (1980-1987) 716.0 Dermatomyositis, 716.1 Polymyositis
   - ICD- 9 (1987-1998) 710 Diffuse collagen tissue Disase, 710.3 DM, 710.4 polymyositis
   - ICD-10 (1998→) M33 Dermatopolymyositis (M 33.0 JDM, M33.1 other DM, M.33.2 PM, M.33.9 unspecified Dermatopolymyositis)

2. The Departments of Pediatrics and Rheumatology at other hospitals previously called "regional hospitals" in Norway.
   These hospitals were contacted by letter and asked to refer any JDM patients they had seen in the period 1995-2005. - *4 patients identified*

By these search strategies, 78 patients were identified, of whom 11 were excluded:

- 7 because they did not fulfill the Bohan Peter criteria (but underwent a diagnostic work-up for JDM).
- 4 due to "error-coding".

Thus, 67 of the identified patients fulfilled the inclusion criteria (of whom 63 were alive) (figure 1). These patients were evenly scattered from all Norway (relatively to population figures). A letter with an invitation to participate was sent all patients (or their parents if < 16 years of age); if no answer, one written reminder was sent.

Controls

Because of the wide age variability of our JDM patients (age 4-54 years at follow-up examination), we chose to include controls for parts of the study (papers II and III). Patients and controls were matched by age and sex (on individual level), and for living in rural or not rural area (on a group level). The controls had their permanent address in Oslo or the neighboring county of Akershus. The controls were randomly selected from the National Population Register by Ergo Group AS, a company which has license to conduct such searches. For each patient, a list of 8-10 possible controls was provided.

A letter with an invitation to participate was sent to the first of the 59 controls on the list (or to the parents if aged < 16 years); if no answer a letter was sent to the

next selected control etc. No written reminders were sent. Because running out of time, at the end of the project, letters was sent to 2-3 individuals at a time. A total of 243 individuals were contacted (figure 1).

The main reason to include controls was to investigate the impact of having the disease JDM on different outcomes. Since some of our JDM patients also had comorbid conditions which could influence the outcomes, we wanted our controls to be representative for the general population; not requiring them to be “perfectly healthy”. However, we made certain exclusion criteria. All responders (or their parents if < 16 years of age), were telephone interviewed before inclusion (by HS).

Exclusion criteria:

- Mobility problems
- Inflammatory rheumatic disease
- Other autoimmune diseases treated with immunosuppressive agents
- Heart or lung disease (except for mild asthma)

10 responders were excluded

- 5 because of presence of exclusion criteria
- 5 because we identified 2 matched controls for 5 patients; the last responder to answer was excluded.

Written informed consent was given from all participants, and from their parents if aged < 16 years. The study was approved by the Regional Committee for Medical Research. The health directory allowed us to use data on dead patients.

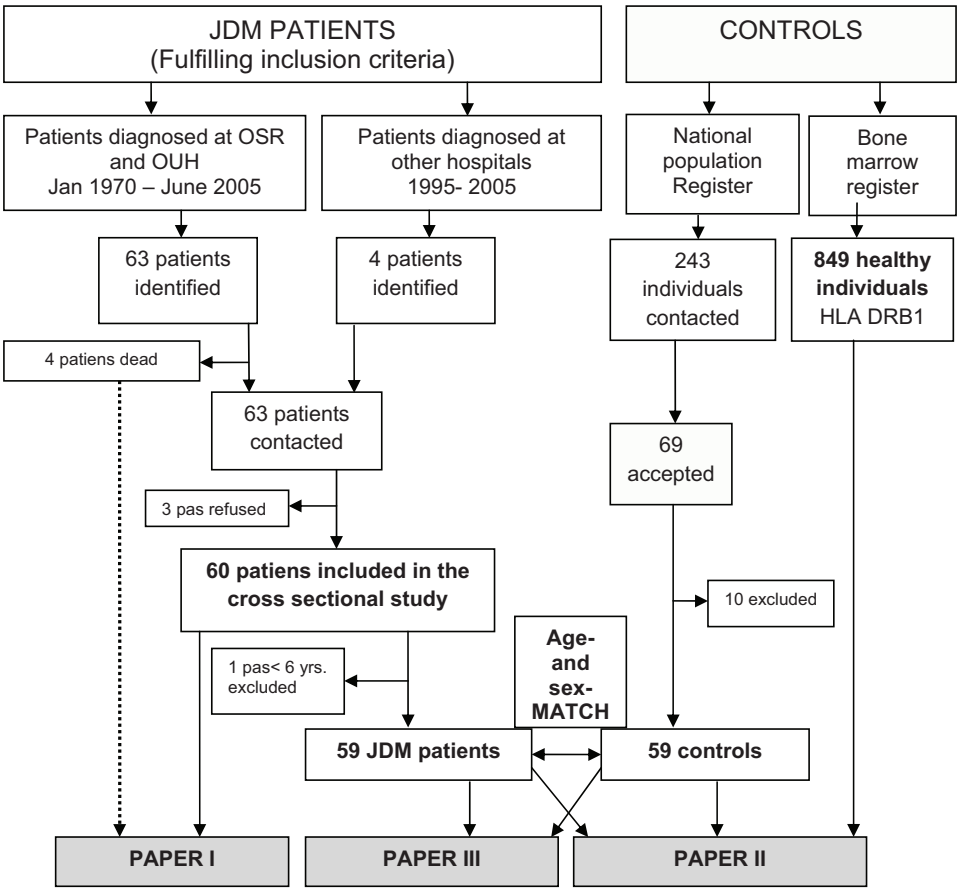

Figure 1. Patients and controls in papers I-III.

Core sets

The core sets for myositis outcome measures, developed by IMACS and PRINTO, guided us in the selection of methods for the study.

Table 4: Outcome domains and core sets for IIM / JDM as proposed by IMACS and PRINTO, and chosen methods for the present thesis.

Domains Core sets	**IMACS (75;79)** *All IIM, including JDM*	**PRINTO (67;98)** *For JDM*	**Present thesis**
1. Disase activity			
Muscle strength	MMT	CMAS (or MMT)	CMAS + MMT *(paper II-III*)
Global disease activity/ Extra muscular assessment	MDAA (DAS)*	DAS (MDAA)	DAS *(papers I-III)*
Functional ability	CMAS or Child-HAQ / HAQ	Child-HAQ	CMAS *(paper II-III)* Child-HAQ/ HAQ (papers I-III)
Muscle enzymes	2 of (CK, ALT, AST, LD, aldolase)	*	CK, ALT, AST, LD *(papers I-III)*
Physicians global	VAS / Likert	VAS	‡ (VAS)
Patients global	VAS / Likert	VAS	‡ (VAS)
Health-related quality of life	(separate domain)	CHQ physical summary score	‡
2. Disase damage			
Muscle strength	MMT	CMAS	CMAS + MMT *(paper II-III)*
Global damage	MDI	MDI	MDI *(papers I-III)*
Functional assessment	Child-HAQ / HAQ*	Child-HAQ	Child-HAQ / HAQ* *(papers I-III)*
Growth and development	_	Height, weight, menses, tanner puberty stage	Height *(paper I-III, but not as outcome)* ‡ tanner puberty stage
Physicians global	VAS / Likert	VAS / Likert	‡
Patients global	VAS / Likert	_	‡
3. Health related quality of life			
	SF-36* (short form 36) CHQ	*(included in disease activity)*	SF-36* (papers *II and III)*

***** Recommended used in clinical studies, but not included in the core sets; ‡ Data collected at follow-up visit, but not included in the present thesis. MDAA = Myositis disease activity assessment tool

Data collection

Chart review

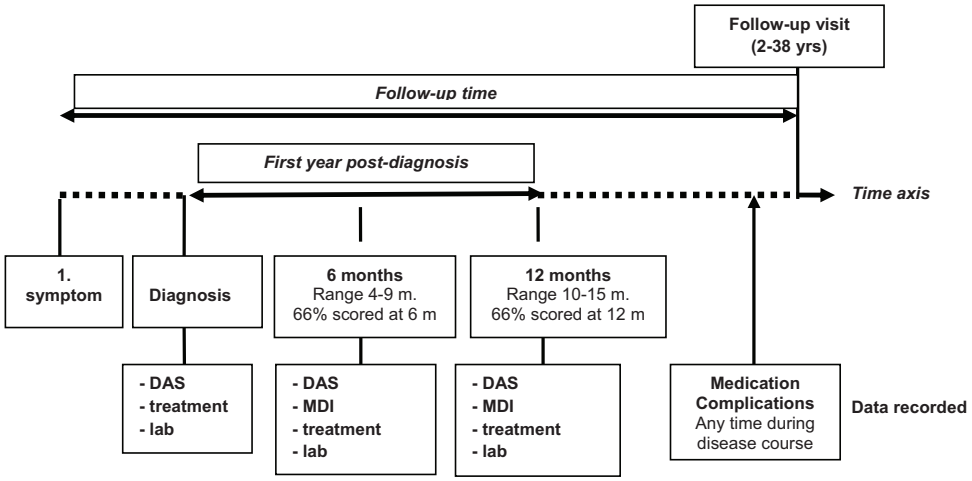

Figure 2. Disease variables collected by chart review

A chart review was carried out in all patients, before the follow-up visit (by HS). If the charts were insufficient, other hospitals were contacted for chart copies. Since we were especially interested in identifying early predictors of unfavorable outcomes, special focus was made on the first year post-diagnosis. Also, the data were found to be most complete from these time-points. In addition, complications (e.g. fractures, calcinosis and lung disease) and use of mediation any time during disease course were recorded. Cumulative prednisolone dose was calculated from the entire disease course; if the data were insufficient, the minimum possible dose was registered. Methylprednisolone was not included in the cumulative dose.

Disease activity (DAS) and organ damage (MDI) were scored retrospectively (by HS). No formal intra-rater reliability testing was performed, but to assure consistency of the scoring, the first charts to be scored were rescored at the end (by HS), with almost identical results.

Follow-up visit

One follow-up visit was carried out of all patients and matched controls in the period September 2005 - December 2009 (figure 3).

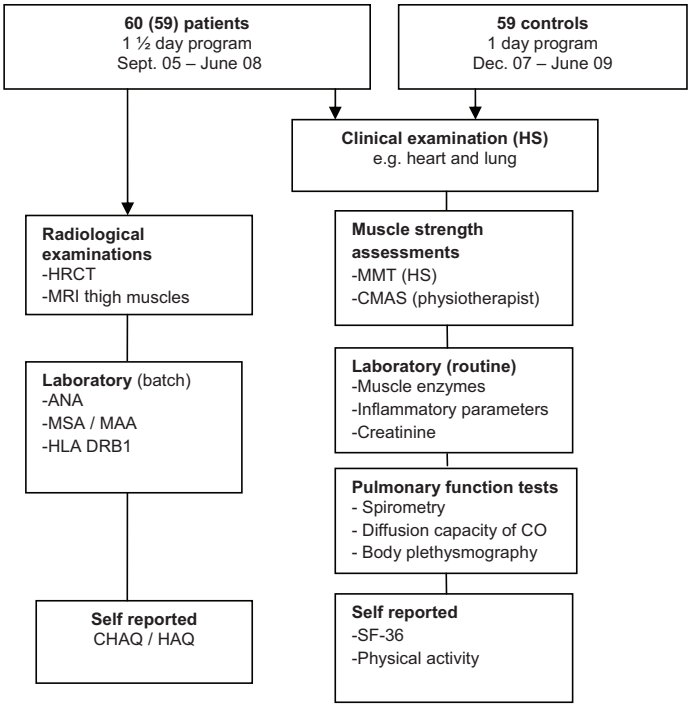

Figure 3. Follow-up assessments in patients and controls

It should be noted that the patients and controls underwent more examinations than listed here (e.g. capillaroscopy, bone mineral density and cardiac examinations, but the results of these examinations are not included in the present thesis.

Disase activity

DAS was chosen for assessment of disease activity (papers I-III). DAS is the preferred instrument to measure for global disease activity by PRINTO (98). Also, even though not included in the disease activity core set by IMACS, the tool is now recommended used in juvenile and adult myositis studies (79). DAS was found to be applicable on retrospective data (as opposed to the alternative global disease activity tool, MDAA, which was not found suitable for retrospective scoring due to its complexity). DAS was scored at the follow-up visit (based on clinical examination)

and at diagnosis, and 6 and 12 month's post-diagnosis (by chart review)(figure 2). If an item was not mentioned in the charts, a score of 0 = absent was given. DAS assesses the extent and distribution of skin involvement and vasculopathic manifestations (DAS skin, range 0-9) and muscle weakness and functional status (DAS muscle, range 0-11). Thus, DAS total has a possible range of 0-20 (were 0 = no activity).

Global organ damage

For assessment of global organ damage, MDI was chosen, as recommended by IMACS and PRINTO (papers I-III) (67;75). The MDI consists of a *total extent of damage score*, were each symptom or sign is scored present or absent, and then summed (range 0-35/37 depending on age and gender). The MDI also consists of Visual Analog Scales (VAS) for all 11 organ/systems, and the sum of these scores makes the *total severity of damage score* (range 0-110). For the present thesis, only *total extent* of damage was chosen. Damage is defined as persistent or permanent changes, being present for at least 6 months. However, during scoring, we became aware that in some patients, evidence of damage during disease course was present (e.g. calcinosis), but the damage item was not clinically apparent at the follow-up examination. We therefore chose to score damage as *cumulative* (present during disease course) in addition to *actual* (clinically present at follow-up) (Paper I). Also, MDI was scored retrospectively at 6 and 12 months post-diagnosis (by chart review) (figure 2). If an item was not mentioned in the charts, it was scored as absent.

Patient reported outcomes

HAQ and Child HAQ were used to measure functional ability in patients aged ≥ 18 years and < 18 years, respectively (paper I-III). Child-HAQ is validated for use in JDM (99;100). Eight areas of daily activities are scored (range 0-3, were 0 means no difficulty with daily activities). Being a disease specific instrument, CHAQ/HAQ was not assessed in matched controls.

Health related quality of life was measured by the Norwegian version of Short Form-36 Health Survey (SF-36) version 1.0, in patients and controls ≥age 12 years (101;102) (papers II and III). SF-36 consists of the Physical Component Summary score (PCS) and the Mental Component Summary score (MCS); both scores have a

mean of 50 in the US population; higher scores indicate better health related quality of life.

Muscle strength

MMT, a validated tool for muscle strength (66) was assessed in all patients and matched controls (by HS) as described in paper II. The MMT-8 version (eight muscle versions applied on right side), grade 0-10 was chosen. The muscles included were: deltoid, biceps, wrist extensors, quadriceps, ankle dorsiflexors, neck flexors, gluteus medius and gluteus maximus. The instructions were adjusted to the patient's age and preformed as shown in the instruction video at IMACS homepage (79).

CMAS was used to evaluate muscle strength, physical function and endurance in children with JDM (80;81). CMAS is recommended as a tool for muscle strength by PRINTO (98), and for functional ability by IMACS; we chose to refer to CMAS as a measure of muscle strength/endurance. CMAS has not been validated in JDM patient's aged ≥ 18 years. CMAS was performed in all patients and 56/59 controls by one of two physiotherapists, who were (as far as possible) blinded to clinical information.

The MMT/CMAS examiners were blinded to each others scores, but could not be blinded to whether the participants were patient or control. Our definition of muscle weakness/reduced endurance (according to MMT and CMAS), was based on the scores in the healthy controls, and was defined as: < mean – 2SD of MMT/CMAS in matched controls (no established cut-off levels applying these tools are available).

Pulmonary function test

Pulmonary function tests (PTF) was performed as described in paper III. All PFT (in children and adults) were measured in the same lab (lung function unit), in order to ensure the consistency of the data. Spirometry (dynamic lung volumes) and diffusing capacity was carried out in all patients and matched controls (applicable in children > 5-6 years of age)(103). Since the literature have reported restrictive ventilatory defects in JDM, body plethysmography (static lung volumes) where included in participants aged ≥ 9 years (applicable in children > 8-10 years) (103). All lung function measurements were performed according to published guidelines (104-106), and established cut-offs (< 5^{th} percentile of the predicted values) for lung function

impairments were chosen (107). All participants were given written instruction not to smoke the last hours before PFT. All DLCO variables were corrected for hemoglobin.

Radiological Examinations

MRI thigh muscles

MRI thigh muscles (T1-weghted and STIR series) were carried out in 58/59 patients as described in paper II. All MRI scans were visually and independently scored by two experienced radiologist, who were blinded to clinical information; in cases of disagreement, consensus was made. Given the long-term follow-up in our patients, special focus was made assessing MRI detected *damage*, which was defined as at least one of the following: calcinosis/fibrosis in muscle or fascia (referred to as calcinosis), muscle atrophy or muscle fatty infiltration. Since no established scoring system for muscular damage is available, a protocol was made by our radiologists (EK and EM), based partly on scoring systems previously used (83;86;108;109)(Rider, Lisa, personal communication). Due to limited availability and practical considerations, MRI scans were not performed in our matched controls.

HRCT thorax

HRCT was carried out in 57/59 patients as described in paper III. All HRCT scans were visually assessed by one experienced radiologist, blinded to clinical information. The scans were evaluated for established HRCT abnormalities (110) according to a standardized protocol (paper III). HRCT is regarded a low dose technique, the dose of radiation was calculated to 0.1- 0.2 mSvb for children and 0.2-1.0 mSvb for adults. For comparison, the annual natural background radiation is 4.5 mSvb (111). HRCT scans were not preformed in the matched, healthy controls, due to ethical considerations. Also, given the relatively young cohort studied, limited HRCT abnormalities would be expected in the general population.

Laboratory measures

The following blood samples were analyzed consecutive (in routine setting) in 59 patients and controls: Hemoglobin, muscle enzymes (CK, LD, ASAT and ALAT), ESR and creatinine.

For detection of ANA, sera from 59 patients were tested at the follow-up visit in a routine diagnostic set-up with indirect immunofluorescence using HEp2 or HEp2000 cells and fluorescein-labeled anti-human IgG (light +heavy chain). Positive samples were titrated and fluorescence patterns interpreted. MSA and MAA were analyzed as batch in sera drawn from 59 patients at the follow-up visit, with a commercial assay Euroline Myositis Profile (Euroimmune, Lübeck, Germany) according to the manufacturer's instructions The kit contained nitrocellulose strips dotted with purified native (Jo-1) or recombinant antigens (Mi-2, Ku, PM-Scl, PL-7, PL-12 and Ro52). In addition a separate line blot strip coated with recombinant SRP, EJ and OJ antigen in three different dilutions was kindly supplied by Euroimmune as a gift. In the first reaction step the strips were incubated with diluted patient sera and in the second step the alkaline phosphatase-labelled goat anti-human IgG was applied (paper II).

DNA was extracted from peripheral blood samples in 59 patients (drawn at the follow-up visit), and DRB1 genotyping was performed by sequencing, as described in paper II. DRB1 data from 898 healthy individuals from the Norwegian bone marrow registry (genotyped by the same method), were used as a control group.

Statistical approach

These are throughout described in the papers, and will not be repeated. All test used in this thesis were two-tailed. In order to explore differences between patients and age- and sex-matched controls in paper II-III, paired statistics were chosen. Corrections for multiple comparisons were not preformed.

7. Summaries of results

Paper I

In order to investigate the extent of and risk factors for organ damage and calcinosis in longstanding JDM, MDI was assessed in 60 JDM patients after median 16.8 (range 2-38) years of follow-up. Early disease variables were assessed by chart review, and disease activity (DAS) and organ damage (MDI) were scored retrospectively from the first year post-diagnosis.

Cumulative organ damage in at least one organ (MDI>0) was found in 90% of the patients at follow-up. Damage occurred most often in the cutaneous (77%), muscular (65%) and skeletal (57%) domains; 47% had calcinosis during disease course. Disease activity decreased during the first year post-diagnosis, whereas cumulative organ damage increased from one year post-diagnosis through follow-up. Early predictors of organ damage were high disease activity (DAS) and damage present (MDI) 6 months post-diagnosis. Follow-up time also correlated with MDI. Calcinosis was predicted by male gender and high disease activity 6 months post-diagnosis.

These results show that the majority of JDM patients have organ damage after median 16.8 years, and that sustained early disease activity predicts such damage.

Paper II

In order to investigate JDM muscular outcome and risk factors for unfavorable outcomes, muscle strength/endurance (MMT and CMAS), laboratory tests (muscle enzymes and creatinine) and health status (SF-36) were assessed in 59 JDM patients and 59 age- and sex-matched controls from the general population. In JDM patients, MRI scans of the thigh muscles were performed. Early disease variables were assessed by chart review. In order to identify predisposing factors for JDM, HLA-DRB1 alleles were determined in all patients and 898 healthy controls.

Muscle strength/endurance and physical health was lower in patients than controls. Muscle weakness/reduced endurance were found in 31% according to CMAS and 42% according to MMT. MRI detected muscular damage was found in 52% of the patients, and included atrophy, fatty infiltration and calcinosis. The outcomes in JDM patients were predicted by high muscular disease activity (DAS)

and muscle damage present 1 year post-diagnosis. Patients had increased HLA-DRB1*0301, and supports this allele as a predisposing genetic factor. Also, a novel association with DRB1*1401 was found in the patients, which needs to be confirmed in larger datasets.

These results show that JDM patients many years after diagnosis have more muscle weakness and poorer physical health compared to the general population, and that sustained early disease activity predicts an unfavorable muscular outcome.

Paper III

In order investigate pulmonary outcome in JDM, pulmonary function (spirometry, measurements of gas diffusion and body plethysmography) was assessed in 59 JDM patients and 59 age- and sex-matched controls from the general population; also HRCT scans were carried out in the JDM patients.

JDM patients had smaller lung volumes (lower total lung capacity, TLC) and lower DLCO than controls. Of JDM patients, a restrictive ventilatory defect was found in 26%, reduced pulmonary diffusion capacity in 49% and HRCT abnormality in 37%. A low TLC was associated with HRCT abnormalities. HRCT abnormalities were associated with restriction, cumulative organ damage and poorer self reported health status at follow-up. None of the pulmonary outcomes correlated with muscle strength. Early disease activity was not found to be predictor of unfavorable pulmonary outcome.

These results show that many JDM patients have impaired lung function and HRCT abnormalities after median 16.8 years of follow-up. Although the findings in many patients were subclinical, our findings highlight the systemic nature of JDM.

8. General Discussion

The first part of the discussion will focus on the representativeness of the patients and controls. Then, the outcomes will be discussed, according to the proposed core sets for myositis outcomes; *disease damage*, *disease activity* and *patient reported health status*. Muscular and pulmonary outcomes will be discussed separately, since muscle strength is included in both activity and damage core sets, whereas pulmonary assessment is not included in any core sets. At last, the early predictors of all the outcomes will be discussed.

The representativeness of the study populations

JDM patients

The selection of patients for our study was based on all Norwegian JDM cases we were able to identify from hospital records in the given time period (*retrospective inception cohort*). The main search for JDM patients was done at the Department of Rheumatology at OUH (including charts from OSR), which is a tertiary center. In addition, some patients treated at the other 3 major hospitals (previously called Regional hospitals) the last 10 years were recruited. Our patients were evenly scattered from all Norway, relatively to population figures. Due to the rareness of the disease, we did not attempt to identify patients who had exclusively been treated at local hospitals or by practitioners. Thus, our patient cohort is referral based, and not population based.

The 67 patients identified from 1970-2006, correspond to an average annual incidence of JDM in Norway of 1.8 / million children < 18 years, which is slightly less than the incidence reported in 2 population based studies (1.9 - 3.2 per million children) (19;20). The 21 identified patients diagnosed from 2000-2006, correspond to an average annual incidence of 2.9 per million children. Taken together, we might be biased towards more severe cases, especially for the earliest diagnosed patients, but our figures support that the majority of Norwegian JDM patients from this time period actually were identified. A major strength of our study is that all living identified patients could be localized (due to the Norwegian population register), and that 95% of those chose to participate in the study. Some other outcomes studies have been limited to patients still followed because of a JDM diagnosis (*prevalence cohort*) (70).

The female predominance, duration of untreated disease and onset features are comparable with other JDM cohorts, whereas the age at diagnosis is slightly higher in our cohort (tables 2+5). Also, our study support HLA DRB1*03 as a predisposing genetic factor (32;36).

Table 5. Patients and disease characteristics at onset in selected JDM cohorts

	Ramanan 2002 (9)	Pachman 2006 (112)	McCann 2006 (8)	Sato 2009 (113)	Rider 2009 (114)	Ravelli 2010 (115)	Sanner papers I-III
Country Source	Canada Hospital	USA Hospital	UK Registry	Brazil Multi center registry	12 centers, USA, Canada and Europe	27 centers, 5 countries, 2 continents	Norway Hospital
Patients included	105 JDM	166 JDM	175 JDM	189 IIM (173 JDM)	143 IIM (134 JDM)	446 JDM	60/59 JDM
Time of diagnosis	1991-2002	1994-1999	Before 2000 retr		1993-2002	1980-2004	1970-2006
European /white/ Caucasian %		74	83	65	65		97
Females %	68	66	69		66	66	60
Age at onset, years (range)		7.5 (3.8)	Mean 7.7 (1-16)	Median 7		Mean 6.9 (0.9-17.8)	Median 7.7 (1.4-17.3)
Age at diagnosis, years (range)					Median 6		Median 8.5 (2.2-19.2)
Untreated disease, months (range),		Median 4 (0-98)	Median 3 (0-118)		Median 3		Median 4 (0-119)
Weakness, %	95	92	88	96		85	97
Heliotrope, %	83			84		62	78
Gottron, %	91		88	83		73	78

If not otherwise stated, these studies have used age limit < 18 years at diagnosis. *age limit < 16 years at diagnosis, † age limit not specified

Matched controls

The randomly selection of our matched controls from the Norwegian population register, is a strength of our study (paper I and II). The age at follow-up is highly variable in our patient cohort. Since the outcome variables studied (e.g. pulmonary function and muscle strength), are highly dependent on sex and age, we wanted to reduce the influence of these factors as possible confounders, and chose a *case* -

control design matching for age and sex. We selected the controls from the "general population", and we thus believe that the detected differences found between controls and patients mainly are due to the presence of JDM. The acceptance rate of the controls was 28%; how this influences the representativeness of the controls we do not know, since we have no information about the non-responders. Our controls had their address in Oslo and the neighboring county of Akershus as opposed to the patients who were settled in all Norway. The population in Norway is relatively homogeneous; also the percentage of European participants was identical in the patient and matched control group. One could suspect that those who volunteer to participate in studies are healthier than others. However, our controls are comparable with the general Norwegian population < 55 years, with regards to dally smoking habits (~ 20%) (116).

Disease damage

All papers included in this thesis, showed that a majority of JDM patients develop organ damage during disease course. This is supported by the findings that 90% of our patients had signs of organ damage in at least one organ (MDI>0) (paper I), that the majority of patients has organ specific damage like muscular damage on MRI (paper II) and impairments of pulmonary function and/or HRCT changes (paper III).

The impact of follow-up time on accumulated damage

When assessing any damage item accumulated from disease onset (e.g. calcinosis or pulmonary fibrosis), the frequency of damage will increase with the length of time a cohort has been studied (74). This is supported by our findings that MDI and MRI detected muscle damage correlated with follow-up time, and that the mean time for development of calcinosis was 2.5 years from disease onset (paper I*).* In order to make studies addressing JDM organ damage comparable, evaluation should ideally cover a minimum follow-up period for all patients (for example at least 2 after symptom onset) and include only patients who have reached this end-point. Patients followed shorter, may still be subjected to develop organ damage (from ongoing disease activity, medication or comorbid conditions). Some of the reported outcome studies include patients followed less than 1 year. We have the longest follow-up time reported (114;115). This also implies that we have included patients who were diagnosed in a period were the treatment regimes were less aggressive, and thus

may have been subjected to more damage, compared to other recent published studies.

Comparison of studies assessing organ damage by MDI

No study applying the MDI tool was available when our study was initiated. Then, during a three months period, two multinational, multicenter, studies addressing JDM organ damage in addition to our paper I, were published (114;115)(Table 5). Damage detectable in at least one organ system was found in 73% of juvenile IIM (Rider, extent score), 69% of JDM patients (Ravelli, severity score) and 90% of JDM patients (paper I, extent score). The follow-up time in the two multinational studies (~ 7 years) is less than half of our study (~ 17 years), which might explain some of these differences, as previously discussed.

The IMACS study is primarily a validation study, and the representativeness of the cohort (recruited from 12 centers in 2 continents) is not discussed. Also, the MDI was exclusively scored based on retrospective data, whereas we scored damage based on chart review and clinical examination. It is possible that mild changes (e.g. cutaneous scarring) were missed if not specifically looked for. In our study, most patients with MDI extent of damage = 1, only had cutaneous scarring. Interestingly, in the IMACS study, damage was found in 98% of the adult IIM patients. If this is due to more comorbid disease in adults (which is also included in MDI), difference in how the method was applied (adult patients were all from US), or if the adult onset disease actually leaves patients with substantial more damage, remains to be settled.

In all these studies, the 3 organs with most often scored damage were (in declining order) skin, muscle and skeletal, which emphasize that skin and muscle are organs most often affected in JDM. We found higher percentages with damage in all these organs compared to Rider and Ravelli. However, these figures are not directly comparable, since we chose to present the extent of damage score also for the 11 organs/systems, as opposed to Rider and Ravelli who used VAS severity score. We scored damage based on chart review 6 and 12 months post diagnosis, and found extent easier to score than severity. Rider validated MDI, and found that the MDI severity and extent scores had a high correlation (r_s = 0.87), and thus may be redundant measures. However, the severity score showed a stronger correlation with other disease measures than the extent score. Indeed, some of the correlations

between MDI and other disease measures were higher in IMACS study than in our study, which may be explained by the fact that we used the extent score.

On the other hand, the scores for the specific items (absent/present) are directly comparable, and our patients had more damage especially in the muscle items (table 5), which will be further discussed under muscular outcome. Calcinosis was also ore often scored in our cohort, 47% cumulative and 37% actual as opposed to ~ 25% in the Ravelli/Rider studies (114;115). However, in the Rider study, it was not specified if the scoring was cumulative. The frequency of calcinosis in our cohort is comparable with some other studies and higher than in others (68) (table 3). This may indicate that we are biased towards severe cases. However, the argument of follow-up time is also important here; e.g. in the Sallum study, 11/35 (31%) of the patients had a follow up time of 2.5 years or less compared to 5% in our study.

Joint contractures were also more frequently scored in our cohort, 53% cumulative and 45% actual, compared to 18-27% (Ravelli/Rider). We scored contractures as fixed limitation in the normal range of motion (as recommended in the glossary term). How this was interpreted in the other studies, we do not know, but we cannot rule out that the discrepancy is due to in how the method was applied. Also, joint contractures may be secondary to calcinosis, which may contribute to the high percentage in our study. Half of our patients had arthritis during disease course (paper I), which is in accordance with a recent published study (117), and might contribute to this high percentage. On the other hand, we did not find any damage in the ocular system, but it should be noted that we did not specifically test vision.

Table 5. JDM outcome studies measuring organ damage by MDI

		Rider for IMACS (114)		Ravelli (115)†	Sanner (paper I)
Patients included		143 IIM (134 JDM)	96 **adult IIM** * (38 DM)	462 JDM	59 JDM
Scoring of MDI		Retrospective	Retrospective	Retr + follow-up cumulative	Retr + follow-up cumulative
Follow-up time, years (range)		Median 6.8 (4.3-8.7)	Median 5 (3.3-8.6) y	Mean 7.7	Med 16.8 (2.0 – 38.1)
Extent of total damage >0, %		**73**	**98**	**63**	**90**
Muscle	Muscle atrophy	11	83	24	35
	Muscle weakness	27	74	11	47
	Muscle dysfunction	23	84	16	42
Skeletal	Joint contracture	27	7	18	53
	Osteoporosis	11	12	6	8
	Avascular necrosis	4	6		5
	Arthropathy	4	18		2
Coetaneous	Calcinosis	26	16	24	47
	Alopecia	5	15		0
	Cutaneous scarring	30	27	44	63
	Poikiloderma	4	8		2
	Lipodystrophy	11	2	10	17
Gastro intestinal	Dysphagia	13	53	5	7
	GI dysmotility	8	37		3
	GI infarction / resection	1	1	2	0
Pulmonary	Dysphonia	15	21		3
	Impaired lung function	4	49		8
	Pulmonary fibrosis	1	28		5
	Pulmonary hypertension	1	4		0
Cardio-vascular	Hypertension	3	29		7
	Ventricular dysfunction	1	21		2
	Angina	NA	1		3
	Myocardial infarction	NA	2		3
Peripheral vascular	Tissue pulp loss	1	1		7
	Digit loss	0	1		3
	Thrombosis	1	3		0
	Claudication	NA	3		0
Endocrine	Growth failure	14	NA	8	10
	Hirsutism	8	2	10	20
	Irregular menses	1	3		20
	Amenorrhea	0	3		8
	Diabetes	1	16		0
Ocular	Cataract	2	10	2	0
	Vision loss	1	2		0
Infection	Chronic	3	14		0
	Multiple	3	2		13
Malignancy		0	3		2

For the specific damage items, numbers are % of total with positive scores

* adult patients from one center in USA, † many items not given, ‡ Infertility, sexual dysfunction and delay in sexual characteristic not listed, due no missing data in all studies.

Disease activity

In the present thesis, we did not use disease activity as a primary outcome measure, but focused on the change in disease activity from the first year post-diagnosis through follow-up (paper I), and also used early disease activity as a predictor for unfavorable outcomes (paper I-II). The level of the DAS scores at diagnosis and during the first year post-diagnosis is comparable with previous studies (58;118;119). We found that DAS skin decreased less compared to DAS muscle during the first year. This is in accordance with a recent study showing that improvement of skin signs seems to be a slow process in parallel with the regeneration of capillary end row loops, whereas muscle inflammation responds more quickly to treatment (58). A register based study, has also showed that more patients have sustained rash than muscle weakness one year after the diagnosis (8). We believe this supports the validity of our retrospective scoring of DAS.

At follow-up, DAS was scored based on clinical examination. A problem with applying DAS after such a long follow-up time, is that DAS does not distinguish between muscle weakness due to disease activity or damage (DAS scoring instructions on IMACS homepage) (79), (Pachman, Lauren M, personal communication). Also, atrophic changes are included in DAS skin. Thus, it might be that disease damage interferes with disease activity when DAS is applied after a long follow-up time. This is supported by that only 30% of our patients used immune suppressive medication at follow-up, whereas > 60% had a DAS > 3 (paper I). Also, MDI and DAS at follow-up correlated (r_s= 0.45) (paper I). Interestingly, Ravelli et al found that more patients had disease activity after mean 7.7 years follow-up according to DAS than according to MDAA, 61% vs. 41%.

Most JDM clinical studies divide their patients into 3 disease courses (monocyclic, polycyclic and chronic continues) or non-unicyclic or unicyclic course (58). However, there are no established remission criteria for JDM. Thus, the definition for ongoing disease (chronic or non-unicyclic disease courses), varies between different studies. Examples of definitions are no detectable clinical, biochemical or radiographic evidence of disease activity and off all medication (52), no evidence of rash, muscle weakness or arthritis, normal muscle enzymes and off all medication for 6 months (120) and DAS ≤ 3 (58). In other studies, duration of

active disease has been calculated without defining disease activity (114;115). Facing problems with the definition of active disease and thus disease courses, we chose not to divide or patients according to these parameters.

Patient reported health status

Table 6. Functional disability in JDM patients

	Huber, 2000	**Sanner 2009***	**Ravelli 2010**
No of patients	67	60	339
Country	Canada	Norway	Multinational
Follow-up time	median 7.2	median 16.8	mean 7.7
No impairment, % of total †,	72	60	59 (Europe 62)
Child-HAQ ≥ 1, % of total	8	3	
Child-HAQ > 1.5, % of total		0	7 (Europe 5)

* HAQ was used in patients > 18 years; † Child-HAQ/HAQ = 0

The majority of our patients had no physical disability as measured by HAQ/Child-HAQ, which is in accordance with previous studies (52;115). However, we had fewer patients with severe impairments than reported in these studies. Child-HAQ/HAQ is included in both disease activity and disease damage core sets. In our study, child-HAQ/HAQ scores, showed a positive correlation with cumulative damage (paper I), MRI detected muscle damage (paper II), and a negative correlation with muscle strength/endurance measured by CMAS and MMT (paper II). Child-HAQ/HAQ scores also showed a positive correlation with HRCT detected abnormality, including HRCT detected ILD and calcinosis (paper III). These findings supports that our outcomes are reflected by patients own perception of the disease. SF-36 PCS was lower in patients than controls supporting impaired physical health related quality of life in the patients. However, no significant difference was found between patients vs. controls, when analyzing patients diagnosed after 1990 separately (paper II).

Muscular outcome

In JDM, muscle weakness may be due to both damage and activity, thus MMT and CMAS are included in both disease activity and damage core sets. Our findings that a substantial portion of patients had muscle weakness at follow-up, is in accordance with Ravelli, who used the same methods to asses muscle strength (CMAS and MMT-8 with identical subsets), a method that recently has been recommended (121).

Our patients had muscle strength comparable to slightly stronger than in the Ravelli study. However, the proportion of patients being though to have muscle weakness due to damage was 4 times higher in our study (47 vs. 11%). This discrepancy may have several explanations. First, according to MDI, the magnitude of muscle weakness necessary in order to be scored is not defined; thus the tools may have been applied differently. Also, we might to a higher degree have interpreted muscle strength impairment to be due to disease damage and not disease activity, especially due to our lengthy follow-up time.

Since we based our cut-off levels for muscle weakness on scores of our matched controls, our cut-offs were lower than those used by Ravelli; when applying these cut-off levels on our patients, we actually found reduced muscle strength in 12-29% of the controls (MMT and CMAS, respectively)(paper II). However, we do not believe that we have identified the ideally cut-offs for muscle weakness applying these tools, for that we would have needed a higher number of controls with a blinded design for patients/controls.

MRI scans were carried out in patients. We included calcinosis in muscle and/or fascia in MRI detected damage, since obviously calcinosis is damage, and when present in these layers, may reduce muscle strength. However, we are aware that MRI is not the preferred method to detect calcinosis, since it might be difficult to distinguish between calcinosis and fibrosis (also being damage), and we did not have radiographic confirmation of density to prove that these changes were calcinosis. However, we believe that the high correlation between “MRI detected muscle damage” and MDI total ($r_s > 0.7$), supports the validity of our scoring.

We found that both CMAS and MMT correlated with MDI muscle damage, whereas only CMAS correlated with MRI detected muscle damage. This may indicate that CMAS to a higher degree than MMT measures damage, which is supported by data from the Ravelli study; Latin American patients had more damage (MDI) and more CMAS impairment, whereas MMT scores comparable. This highlights the importance of measuring muscular endurance. Another tool for measuring endurance, the Functional index has been developed (122;123), but needs special equipment and has not been validated in children.

Pulmonary outcome

Measures for pulmonary outcomes are not included in the core sets for disease activity or damage. However, the pulmonary system is included in MDI. In our study, 17% were found to have pulmonary damage (by MDI) (paper I), a result which is comparable with one study (114) and higher than another (115). Even though previous studies have reported a high frequency of restrictive defects in JDM (72;93), the finding of 25-50 % of the patients having restrictive ventilatory defects or low DLCO after median 16.8 years follow-up, was surprising. Our assessment of restriction was done by body plethysmographic assessed TLC, which is the preferred method. Also, we showed that low lung volumes were associated with HRCT abnormalities.

Pulmonary impairment did not differ between patients diagnosed before or after 1990, but we are aware that we might be underpowered to show such associations. We were neither able to find any correlation between pulmonary function and muscle strength; nor did we identify any early predictors for the pulmonary outcomes. This might indicate that the processes affecting the lungs may differ from the other disease processes.

Prognostic factors for unfavorable outcomes

A major finding of this thesis, is the identification of sustained early disease activity (measured by DAS 6 and 12 months post-diagnosis), as early predictors of calcinosis and cumulative organ damage (paper I), and for MRI detected muscular damage and decreased muscle strength/endurance at follow-up (paper II).

Identification of early predictors of unfavorable outcomes is obviously important. Growing evidence suggest that sustained early disease activity is associated with unfavorable outcomes (Table 7). There is some data suggesting that onset features is associated with unfavorable outcomes (58;115), even though most studies have not shown such associations)(52)(present thesis). One other study have evaluated disease features the first year post-diagnosis, and found that skin rash and nailfold abnormalities were associated with long time to remission, but not with disease course (120). Then again, a long duration of active disease has been found to predict different damage items (115). However, chronic disease course is the predictor most often associated with unfavorable outcome. One can speculate that our findings of sustained disease activity and high MDI during the first year post-diagnosis are markers for a chronic disease course. However, that assumption is not supported by a recent study (58).

Patients' characteristics, especially female gender has recently been associated with unfavorable outcomes. Our finding of male gender as a predictor of calcinosis should thus be interpreted with caution. We were not able to identify treatment variables as predictors, which might be due to *confounding by indication* (seriously affected patients are treated more aggressively*)* (118). Also, duration of untreated disease has been predictive of calcinosis (58); in our study, duration from symptom to diagnosis showed a weak, univariate, but not multivariate association. This may have been due to limited sample size. At last, it is important to be aware of that a statistical correlation not necessarily means a casual connection, and that predictors can be applied at group level, and cannot necessarily predict the outcome in a single patient.

Table 7. Identified early predictors of unfavorable JDM outcomes

Predictor	Outcome	Study
Female	Muscle weakness (MMT)	Ravelli 2010, Sanner (paper II)
	Muscle weakness (CMAS)	Ravelli 2010
	Functional disability (Child-HAQ)	Huber 2000, Ravelli 2010
Male	Calcinosis	Sanner (paper I)
Young age at onset	Muscle weakness (CMAS)	Ravelli 2010
Delayed treatment	Calcinosis	Bowyer 1983, Fisler 2002, Pachman 1998/2005, Tabarki 1998
Long duration untreated disease	Non-monocyclic course	Christen-Zaech 2008
Inadequate treatment	Calcinosis	Bowyer 1983, Fisler 2002
Insidious disease onset	Continued disease activity (DAS, MDAA)	Ravelli 2010
Skin symptoms at onset	Cutaneous damage (MDI)	Ravelli 2010
	Muscle weakness (CMAS)	Ravelli 2010
	Chronic disease course	Christen-Zaech 2008
Skin or GI ulcerations	Organ damage (MDI)	Rider 2009
Muscle weakness at onset	Muscle damage (MDI)	Ravelli 2010
Muscle biopsy findings*	Chronic disease course	Crowe 1982, Wargula 2006, Miles 2007
Anti p155/140	Cutaneous involvement / lipodystrophy	Gunawardena 2008, Bingham 2008
Anti p 140	Calcinosis	Gunawardena 2009
Gottron 3/6 months	Long time to remission	Stringer 2008
Nailfold abnormalities, 6 months	Long time to remission	Stringer 2008
High DAS total 6/12 months	Organ damage (MDI)	Sanner (paper I)
	Calcinosis	Sanner (paper I)
	MRI detected muscle damage	Sanner (paper II)
High DAS muscle, 12 months	Low CMAS	Sanner (paper II)
High MDI, 6/12 months	Organ damage	Sanner (paper I)
MDI muscle damage, 12 months	Low MMT	Sanner (paper II)
	MRI detected muscle damage	Sanner (paper II)
Long duration active disease	Organ damage (MDI)	Rider 2009
	Skin damage (MDI)	Ravelli 2010
	Calcinosis / Lipodystrophy	Ravelli 2010
	Skin damage (MDI)	Ravelli 2010
Chronic disease course	Calcinosis	Bowyer 1983, Ravelli 2010
	Functional disability (Child-HAQ)	Huber 2000, Ravelli 2010
	Organ damage (MDI)	Ravelli 2010
	Muscle weakness (MMT)	Ravelli 2010
	Muscle weakness (CMAS)	Ravelli 2010
	Disease activity (DAS/MDAA)	Ravelli 2010

Studies included: Ravelli 2010 (115), Huber 2000 (52), Bowyer 1983 (45) , Fisler 2002 (53), Pachman 1998 (124), Pachman 2005 (27), Tabarki 1998 (74), Christen-Zaech 2008(58), Rider 2009 (114), Crowe 1982 (125), Wargula 2006 (126), Miles 2007 (127), Gunawardena 2008 (128), Bingham 2008 (129), Gunawardena 2009 (130), Stringer 2008 (120);
*arteropathic changes, capillary loss.

9. Main conclusions

- 90% of JDM patients had cumulative organ damage in at least organ, median 16.8 years after disease onset
- Organ damage was most frequently found in the cutaneous, muscular and skeletal domains
- Disease activity decreased during the first year post-diagnosis, whereas cumulative organ damage increased from 1 year to follow-up.
- JDM patients had lower muscle strength and physical function compared to age- and sex-matched controls from the general population.
- MRI detected muscle damage was found in ~ 50% of the patients, and correlated with cumulative organ damage, and muscle strength/endurance.
- High disease activity and high cumulative damage / muscle damage 6 and 12 months after JDM diagnosis, were identified as early predictors of calcinosis, cumulative organ damage, muscle weakness and MRI detected muscle damage at follow-up.
- JDM patients had lower gas diffusion and smaller lung volumes than controls; restrictive ventilatory defects were found in ~25% and reduced DLCO in ~ 50% of the patients.
- HRCT abnormalities was found in 37% of the patients, and included calcinosis in the chest wall in 14%, interstitial lung disease in 14% and small airways disease in 15%. HRCT abnormalities were associated with restrictive ventilation defects, cumulative organ damage and patient reported outcomes.
- The pulmonary involvement was mostly subclinical and difficult to predict, but highlights the systemic nature of JDM.
- HLA-DRB1* 0301 was confirmed to be a predisposing factor for JDM in Norwegian JDM patients, and HLA-DR*1401 was identified as a possible novel predisposing factor.

Concluding remarks

We have answered some aspects of the question “what is the prognosis of JDM”, by looking at Norwegian patients. We believe that our findings can be generalized to other countries were the treatment regimes are comparable. Increased knowledge about JDM outcomes is important for the patients and their parents, and for the pediatric rheumatologist and other health professionals working with these patients. However, it should be further debated, what are the best methods to measure long-term outcome, since the core sets developed for outcomes in clinical trials might not be ideal for assessing long term outcome.

Our identification of sustained early disease activity as a predictor for unfavorable outcomes, is in accordance with other studies, and might be useful in clinical practice. However, one should be aware that such predictors not necessarily can be applied in a single patient. Our findings of pulmonary impairment should warrant clinicians about the possibility of pulmonary complications also in the juvenile form of DM.

Given the rareness of this disease, we welcome the ongoing international collaborations, making large prospective natural history studies possible. We do however believe that single center studies like ours, have a place in carefully examining patients, by one/few investigator(s). Recently, there have been important new developments in immunology and thus treatment rationale for JDM. International collaborations are also important in exploring the effects of modern treatment on outcomes. Since our study is not mechanistic in nature, we intend to explore mechanisms behind our findings, like micro vascular changes, cytokine profiles, autoantibodies and muscle biopsy finding, in future studies.

10. References

(1) Feldman BM, Rider LG, Reed AM, Pachman LM. Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood. Lancet 2008 Jun 28;371(9631):2201-12.

(2) Bitnum, Daeschner CW, Jr., Travis LB, Dodge WF, Hopps HC. Dermatomyositis. J Pediatr 1964 Jan;64:101-31.

(3) Huber A, Feldman BM. Long-term Outcomes in Juvenile Dermatomyositis: How Did We Get Here and Where Are We Going? Curr Rheumatol Rep 2005 Dec;7(6):441-6.

(4) Lindsley CB. Juvenile dermatomyositis update. Curr Rheumatol Rep 2006 Jun;8(3):174-7.

(5) Rider LG, Miller FW. Classification and treatment of the juvenile idiopathic inflammatory myopathies. Rheum Dis Clin North Am 1997 Aug;23(3):619-55.

(6) Wedderburn LR, Li CK. Paediatric idiopathic inflammatory muscle disease. Best Pract Res Clin Rheumatol 2004 Jun;18(3):345-58.

(7) Pachman LM. Juvenile dermatomyositis: immunogenetics, pathophysiology, and disease expression. Rheum Dis Clin North Am 2002 Aug;28(3):579-602, vii.

(8) McCann LJ, Juggins AD, Maillard SM, Wedderburn LR, Davidson JE, Murray KJ, et al. The Juvenile Dermatomyositis National Registry and Repository (UK and Ireland)--clinical characteristics of children recruited within the first 5 yr. Rheumatology (Oxford) 2006 Mar 27;45:1255-60.

(9) Ramanan AV, Feldman BM. Clinical features and outcomes of juvenile dermatomyositis and other childhood onset myositis syndromes. Rheum Dis Clin North Am 2002 Nov;28(4):833-57.

(10) Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975 Feb 13;292(7):344-7.

(11) Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). N Engl J Med 1975 Feb 20;292(8):403-7.

(12) Oddis CV, Rider LG, Reed AM, Ruperto N, Brunner HI, Koneru B, et al. International consensus guidelines for trials of therapies in the idiopathic inflammatory myopathies. Arthritis Rheum 2005 Sep;52(9):2607-15.

(13) Cassidy JT, Petty RE, Laxer RM, Lindsley CB. Juvenile Dermatomyositis. Textbook of Pediatric Rheumatology. 5 ed. 2005. p. 407-9.

(14) Brown VE, Pilkington CA, Feldman BM, Davidson JE. An international consensus survey of the diagnostic criteria for juvenile dermatomyositis (JDM). Rheumatology (Oxford) 2006 Aug;45(8):990-3.

(15) Tanimoto K, Nakano K, Kano S, Mori S, Ueki H, Nishitani H, et al. Classification criteria for polymyositis and dermatomyositis. J Rheumatol 1995 Apr;22(4):668-74.

(16) Hoogendijk JE, Amato AA, Lecky BR, Choy EH, Lundberg IE, Rose MR, et al. 119th ENMC international workshop: trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis, 10-12 October 2003, Naarden, The Netherlands. Neuromuscul Disord 2004 May;14(5):337-45.

(17) Classification criteria study. 2010. IMACS, International Myositis Assessment & Clinical Studies Group. Ref Type: Online Source

(18) Sultan SM, Isenberg DA. Re-classifying myositis: 30 years on from Bohan and Peter. Rheumatology (Oxford) 2009 Dec 29.

(19) Symmons DP, Sills JA, Davis SM. The incidence of juvenile dermatomyositis: results from a nation-wide study. Br J Rheumatol 1995 Aug;34(8):732-6.

(20) Mendez EP, Lipton R, Ramsey-Goldman R, Roettcher P, Bowyer S, Dyer A, et al. US incidence of juvenile dermatomyositis, 1995-1998: results from the National Institute of Arthritis and Musculoskeletal and Skin Diseases Registry. Arthritis Rheum 2003 Jun 15;49(3):300-5.

(21) Kaipiainen-Seppanen O, Savolainen A. Incidence of chronic juvenile rheumatic diseases in Finland during 1980-1990. Clin Exp Rheumatol 1996 Jul;14(4):441-4.

(22) Darin N, Tulinius M. Neuromuscular disorders in childhood: a descriptive epidemiological study from western Sweden. Neuromuscul Disord 2000 Jan;10(1):1-9.

(23) Pelkonen PM, Jalanko HJ, Lantto RK, Makela AL, Pietikainen MA, Savolainen HA, et al. Incidence of systemic connective tissue diseases in children: a nationwide prospective study in Finland. J Rheumatol 1994 Nov;21(11):2143-6.

(24) Shehata R, al Mayouf S, al Dalaan A, al Mazaid A, al Balaa S, Bahabri S. Juvenile dermatomyositis: clinical profile and disease course in 25 patients. Clin Exp Rheumatol 1999 Jan;17(1):115-8.

(25) Hiketa T, Matsumoto Y, Ohashi M, Sasaki R. Juvenile dermatomyositis: a statistical study of 114 patients with dermatomyositis. J Dermatol 1992 Aug;19(8):470-6.

(26) Medsger TA, Jr., Dawson WN, Jr., Masi AT. The epidemiology of polymyositis. Am J Med 1970 Jun;48(6):715-23.

(27) Pachman LM, Lipton R, Ramsey-Goldman R, Shamiyeh E, Abbott K, Mendez EP, et al. History of infection before the onset of juvenile dermatomyositis: results from the National Institute of Arthritis and Musculoskeletal and Skin Diseases Research Registry. Arthritis Rheum 2005 Apr 15;53(2):166-72.

(28) Gardner-Medwin JM, Dolezalova P, Cummins C, Southwood TR. Incidence of Henoch-Schonlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. Lancet 2002 Oct 19;360(9341):1197-202.

(29) Oddis CV, Conte CG, Steen VD, Medsger TA, Jr. Incidence of polymyositis-dermatomyositis: a 20-year study of hospital diagnosed cases in Allegheny County, PA 1963-1982. J Rheumatol 1990 Oct;17(10):1329-34.

(30) Fujikawa S, Okuni M. A nationwide surveillance study of rheumatic diseases among Japanese children. Acta Paediatr Jpn 1997 Apr;39(2):242-4.

(31) Wedderburn LR, Rider LG. Juvenile dermatomyositis: new developments in pathogenesis, assessment and treatment. Best Pract Res Clin Rheumatol 2009 Oct;23(5):665-78.

(32) Wedderburn LR, McHugh NJ, Chinoy H, Cooper RG, Salway F, Ollier WE, et al. HLA class II haplotype and autoantibody associations in children with juvenile dermatomyositis and juvenile dermatomyositis-scleroderma overlap. Rheumatology (Oxford) 2007 Dec;46(12):1786-91.

(33) Friedman JM, Pachman LM, Maryjowski ML, Radvany RM, Crowe WE, Hanson V, et al. Immunogenetic studies of juvenile dermatomyositis: HLA-DR antigen frequencies. Arthritis Rheum 1983 Feb;26(2):214-6.

(34) Reed AM, Pachman L, Ober C. Molecular genetic studies of major histocompatibility complex genes in children with juvenile dermatomyositis: increased risk associated with HLA-DQA1 *0501. Hum Immunol 1991 Dec;32(4):235-40.

(35) O'Hanlon TP, Carrick DM, Arnett FC, Reveille JD, Carrington M, Gao X, et al. Immunogenetic risk and protective factors for the idiopathic inflammatory myopathies: distinct HLA-A, -B, -Cw, -DRB1 and -DQA1 allelic profiles and motifs define clinicopathologic groups in caucasians. Medicine (Baltimore) 2005 Nov;84(6):338-49.

(36) Mamyrova G, O'Hanlon TP, Monroe JB, Carrick DM, Malley JD, Adams S, et al. Immunogenetic risk and protective factors for juvenile dermatomyositis in Caucasians. Arthritis Rheum 2006 Dec;54(12):3979-87.

(37) Pachman LM, Liotta-Davis MR, Hong DK, Kinsella TR, Mendez EP, Kinder JM, et al. TNFalpha-308A allele in juvenile dermatomyositis: association with increased production of tumor necrosis factor alpha, disease duration, and pathologic calcifications. Arthritis Rheum 2000 Oct;43(10):2368-77.

(38) Lutz J, Huwiler KG, Fedczyna T, Lechman TS, Crawford S, Kinsella TR, et al. Increased plasma thrombospondin-1 (TSP-1) levels are associated with the TNF alpha-308A allele in children with juvenile dermatomyositis. Clin Immunol 2002 Jun;103(3 Pt 1):260-3.

(39) Mamyrova G, O'Hanlon TP, Sillers L, Malley K, James-Newton L, Parks CG, et al. Cytokine gene polymorphisms as risk and severity factors for juvenile dermatomyositis. Arthritis Rheum 2008 Nov 26;58(12):3941-50.

(40) Pachman LM, Hayford JR, Hochberg MC, Pallansch MA, Chung A, Daugherty CD, et al. New-onset juvenile dermatomyositis: comparisons with a healthy cohort and children with juvenile rheumatoid arthritis. Arthritis Rheum 1997 Aug;40(8):1526-33.

(41) Reed AM, Ytterberg SR. Genetic and environmental risk factors for idiopathic inflammatory myopathies. Rheum Dis Clin North Am 2002 Nov;28(4):891-916.

(42) Banker BQ, Victor M. Dermatomyositis (systemic angiopathy) of childhood. Medicine (Baltimore) 1966 Jul;45(4):261-89.

(43) Rennebohm R. Juvenile dermatomyositis. Pediatr Ann 2002 Jul;31(7):426-33.

(44) Walsh JS, Fairley JA. Calcifying disorders of the skin. J Am Acad Dermatol 1995 Nov;33(5 Pt 1):693-706.

(45) Bowyer SL, Blane CE, Sullivan DB, Cassidy JT. Childhood dermatomyositis: factors predicting functional outcome and development of dystrophic calcification. J Pediatr 1983 Dec;103(6):882-8.

(46) Hausmanowa-Petrusewicz I, Kowalska-Oledzka E, Miller FW, Jarzabek-Chorzelska M, Targoff IN, Blaszczyk-Kostanecka M, et al. Clinical, serologic, and immunogenetic features in Polish patients with idiopathic inflammatory myopathies. Arthritis Rheum 1997 Jul;40(7):1257-66.

(47) Hengstman GJ, van BL, Vree Egberts WT, van der Kooi EL, Borm GF, Padberg GW, et al. High specificity of myositis specific autoantibodies for myositis compared with other neuromuscular disorders. J Neurol 2005 May;252(5):534-7.

(48) Feldman BM, Reichlin M, Laxer RM, Targoff IN, Stein LD, Silverman ED. Clinical significance of specific autoantibodies in juvenile dermatomyositis. J Rheumatol 1996 Oct;23(10):1794-7.

(49) Pachman LM. Inflammatory myopathy in children. Rheum Dis Clin North Am 1994 Nov;20(4):919-42.

(50) Huemer C, Kitson H, Malleson PN, Sanderson S, Huemer M, Cabral DA, et al. Lipodystrophy in patients with juvenile dermatomyositis--evaluation of clinical and metabolic abnormalities. J Rheumatol 2001 Mar;28(3):610-5.

(51) Stockton D, Doherty VR, Brewster DH. Risk of cancer in patients with dermatomyositis or polymyositis, and follow-up implications: a Scottish population-based cohort study. Br J Cancer 2001 Jul 6;85(1):41-5.

(52) Huber AM, Lang B, LeBlanc CM, Birdi N, Bolaria RK, Malleson P, et al. Medium- and long-term functional outcomes in a multicenter cohort of children with juvenile dermatomyositis. Arthritis Rheum 2000 Mar;43(3):541-9.

(53) Fisler RE, Liang MG, Fuhlbrigge RC, Yalcindag A, Sundel RP. Aggressive management of juvenile dermatomyositis results in improved outcome and decreased incidence of calcinosis. J Am Acad Dermatol 2002 Oct;47(4):505-11.

(54) Blane CE, White SJ, Braunstein EM, Bowyer SL, Sullivan DB. Patterns of calcification in childhood dermatomyositis. AJR Am J Roentgenol 1984 Feb;142(2):397-400.

(55) Moore EC, Cohen F, Douglas SD, Gutta V. Staphylococcal infections in childhood dermatomyositis--association with the development of calcinosis, raised IgE concentrations and granulocyte chemotactic defect. Ann Rheum Dis 1992 Mar;51(3):378-83.

(56) Spencer CH, Hanson V, Singsen BH, Bernstein BH, Kornreich HK, King KK. Course of treated juvenile dermatomyositis. J Pediatr 1984 Sep;105(3):399-408.

(57) Miller LC, Michael AF, Kim Y. Childhood dermatomyositis. Clinical course and long-term follow-up. Clin Pediatr (Phila) 1987 Nov;26(11):561-6.

(58) Christen-Zaech S, Seshadri R, Sundberg J, Paller AS, Pachman LM. Persistent association of nailfold capillaroscopy changes and skin involvement over thirty-six months with duration of untreated disease in patients with juvenile dermatomyositis. Arthritis Rheum 2008 Jan 31;58(2):571-6.

(59) Zipitis CS, Baildam EM, Ramanan AV. Treatment approaches to juvenile dermatomyositis. Expert Opin Pharmacother 2004 Jul;5(7):1509-15.

(60) Ramanan AV, Campbell-Webster N, Ota S, Parker S, Tran D, Tyrrell PN, et al. The effectiveness of treating juvenile dermatomyositis with methotrexate and aggressively tapered corticosteroids. Arthritis Rheum 2005 Nov;52(11):3570-8.

(61) Maillard SM, Jones R, Owens CM, Pilkington C, Woo PM, Wedderburn LR, et al. Quantitative assessments of the effects of a single exercise session on muscles in juvenile dermatomyositis. Arthritis Rheum 2005 Aug 15;53(4):558-64.

(62) World Health Organization. The International classifications of functioning, disability and health. 2001. Ref Type: Online Source

(63) Stamm T, Machold K. The International Classification of Functioning, Disability and Health in practice in rheumatological care and research. Curr Opin Rheumatol 2007 Mar;19(2):184-9.

(64) Lundberg IE, Alexanderson H. Technology insight: tools for research, diagnosis and clinical assessment of treatment in idiopathic inflammatory myopathies. Nat Clin Pract Rheumatol 2007 May;3(5):282-90.

(65) Duffy CM. Health outcomes in pediatric rheumatic diseases. Curr Opin Rheumatol 2004 Mar;16(2):102-8.

(66) Miller FW, Rider LG, Chung YL, Cooper R, Danko K, Farewell V, et al. Proposed preliminary core set measures for disease outcome assessment in adult and juvenile idiopathic inflammatory myopathies. Rheumatology (Oxford) 2001 Nov;40(11):1262-73.

(67) Ruperto N, Ravelli A, Murray KJ, Lovell DJ, Andersson-Gare B, Feldman BM, et al. Preliminary core sets of measures for disease activity and damage assessment in juvenile systemic lupus erythematosus and juvenile dermatomyositis. Rheumatology (Oxford) 2003 Dec;42(12):1452-9.

(68) Sallum AM, Kiss MH, Sachetti S, Resende MB, Moutinho KC, Carvalho MS, et al. Juvenile dermatomyositis: clinical, laboratorial, histological, therapeutical and evolutive parameters of 35 patients. Arq Neuropsiquiatr 2002 Dec;60(4):889-99.

(69) Singh S, Bansal A. Rheumatol Int 2006 Apr;26(6):510-5.

(70) Chalmers A, Sayson R, Walters K. Juvenile dermatomyositis: medical, social and economic status in adulthood. Can Med Assoc J 1982 Jan 1;126(1):31-3.

(71) Collison CH, Sinal SH, Jorizzo JL, Walker FO, Monu JU, Snyder J. Juvenile dermatomyositis and polymyositis: a follow-up study of long-term sequelae. South Med J 1998 Jan;91(1):17-22.

(72) Pachman LM, Cooke N. Juvenile dermatomyositis: a clinical and immunologic study. J Pediatr 1980 Feb;96(2):226-34.

(73) Ng YT, Ouvrier RA, Wu T. Drug therapy in juvenile dermatomyositis: follow-up study. J Child Neurol 1998 Mar;13(3):109-12.

(74) Tabarki B, Ponsot G, Prieur AM, Tardieu M. Childhood dermatomyositis: clinical course of 36 patients treated with low doses of corticosteroids. Eur J Paediatr Neurol 1998;2(4):205-11.

(75) Isenberg DA, Allen E, Farewell V, Ehrenstein MR, Hanna MG, Lundberg IE, et al. International consensus outcome measures for patients with idiopathic inflammatory myopathies. Development and initial validation of myositis activity and damage indices in patients with adult onset disease. Rheumatology (Oxford) 2004 Jan;43(1):49-54.

(76) Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996 Mar;39(3):363-9.

(77) Harris-Love MO, Shrader JA, Koziol D, Pahlajani N, Jain M, Smith M, et al. Distribution and severity of weakness among patients with polymyositis, dermatomyositis and juvenile dermatomyositis. Rheumatology (Oxford) 2009 Feb;48(2):134-9.

(78) Hicks J, Wesley R, Koziol D, et al. Prelminary validation of abbreviated manual muscle testing (MMT) in the assessment of juvenile dermatomyositis. Arthritis Rheum 2000;43(Supplement):195.

(79) IMACS website, https:, dir-apps.niehs.nih.gov/imacs/index.cfm?action=home.main. International Myositis Assessment & Clinical Studies Group. 2010. National Institute of Enviromental Health Sciences, Division of Intramural research. Ref Type: Online Source

(80) Lovell DJ, Lindsley CB, Rennebohm RM, Ballinger SH, Bowyer SL, Giannini EH, et al. Development of validated disease activity and damage indices for the juvenile idiopathic inflammatory myopathies. II. The Childhood Myositis Assessment Scale (CMAS): a quantitative tool for the evaluation of muscle function. The Juvenile Dermatomyositis Disease Activity Collaborative Study Group. Arthritis Rheum 1999 Oct;42(10):2213-9.

(81) Huber AM, Feldman BM, Rennebohm RM, Hicks JE, Lindsley CB, Perez MD, et al. Validation and clinical significance of the Childhood Myositis Assessment Scale for assessment of muscle function in the juvenile idiopathic inflammatory myopathies. Arthritis Rheum 2004 May;50(5):1595-603.

(82) Hernandez RJ, Sullivan DB, Chenevert TL, Keim DR. MR imaging in children with dermatomyositis: musculoskeletal findings and correlation with clinical and laboratory findings. AJR Am J Roentgenol 1993 Aug;161(2):359-66.

(83) Kimball AB, Summers RM, Turner M, Dugan EM, Hicks J, Miller FW, et al. Magnetic resonance imaging detection of occult skin and subcutaneous abnormalities in juvenile

dermatomyositis. Implications for diagnosis and therapy. Arthritis Rheum 2000 Aug;43(8):1866-73.

(84) Adams EM, Chow CK, Premkumar A, Plotz PH. The idiopathic inflammatory myopathies: spectrum of MR imaging findings. Radiographics 1995 May;15(3):563-74.

(85) Fraser DD, Frank JA, Dalakas M, Miller FW, Hicks JE, Plotz P. Magnetic resonance imaging in the idiopathic inflammatory myopathies. J Rheumatol 1991 Nov;18(11):1693-700.

(86) Summers RM, Brune AM, Choyke PL, Chow CK, Patronas NJ, Miller FW, et al. Juvenile idiopathic inflammatory myopathy: exercise-induced changes in muscle at short inversion time inversion-recovery MR imaging. Radiology 1998 Oct;209(1):191-6.

(87) Gardner-Medwin JM, Irwin G, Johnson K. MRI in juvenile idiopathic arthritis and juvenile dermatomyositis. Ann N Y Acad Sci 2009 Feb;1154:52-83.

(88) Hilario MO, Yamashita H, Lutti D, Len C, Terreri MT, Lederman H. Juvenile idiopathic inflammatory myopathies: the value of magnetic resonance imaging in the detection of muscle involvement. Sao Paulo Med J 2000 Mar 2;118(2):35-40.

(89) Fathi M, Lundberg IE, Tornling G. Pulmonary complications of polymyositis and dermatomyositis. Semin Respir Crit Care Med 2007 Aug;28(4):451-8.

(90) Gunawardena H, Betteridge ZE, McHugh NJ. Myositis-specific autoantibodies: their clinical and pathogenic significance in disease expression. Rheumatology (Oxford) 2009 Jun;48(6):607-12.

(91) Tosun A, Serdaroglu G, Aslan MT, Polat M, Akalin T, Tekgul H, et al. Severe juvenile dermatomyositis: two patients complicated with extra musculocutaneous involvement. Rheumatol Int 2006 May 24.

(92) Prahalad S, Bohnsack JF, Maloney CG, Leslie KO. Fatal acute fibrinous and organizing pneumonia in a child with juvenile dermatomyositis. J Pediatr 2005 Feb;146(2):289-92.

(93) Trapani S, Camiciottoli G, Vierucci A, Pistolesi M, Falcini F. Pulmonary involvement in juvenile dermatomyositis: a two-year longitudinal study. Rheumatology (Oxford) 2001 Feb;40(2):216-20.

(94) Woo P. Theoretical and practical basis for early aggressive therapy in paediatric autoimmune disorders. Curr Opin Rheumatol 2009 Jul 29.

(95) Padley SP, Hansell DM, Flower CD, Jennings P. Comparative accuracy of high resolution computed tomography and chest radiography in the diagnosis of chronic diffuse infiltrative lung disease. Clin Radiol 1991 Oct;44(4):222-6.

(96) Kobayashi I, Yamada M, Takahashi Y, Kawamura N, Okano M, Sakiyama Y, et al. Interstitial lung disease associated with juvenile dermatomyositis: clinical features and efficacy of cyclosporin A. Rheumatology (Oxford) 2003 Feb;42(2):371-4.

(97) Sullivan DB, Cassidy JT, Petty RE. Dermatomyositis in the pediatric patient. Arthritis Rheum 1977 Mar;20(2 Suppl):327-31.

(98) Ruperto N, Ravelli A, Pistorio A, Ferriani V, Calvo I, Ganser G, et al. The provisional Paediatric Rheumatology International Trials Organisation/American College of Rheumatology/European League Against Rheumatism Disease activity core set for the evaluation of response to therapy in juvenile dermatomyositis: A prospective validation study. Arthritis Rheum 2008 Jan 15;59(1):4-13.

(99) Feldman BM, Ayling-Campos A, Luy L, Stevens D, Silverman ED, Laxer RM. Measuring disability in juvenile dermatomyositis: validity of the childhood health assessment questionnaire. J Rheumatol 1995 Feb;22(2):326-31.

(100) Huber AM, Hicks JE, Lachenbruch PA, Perez MD, Zemel LS, Rennebohm RM, et al. Validation of the Childhood Health Assessment Questionnaire in the juvenile idiopathic myopathies. Juvenile Dermatomyositis Disease Activity Collaborative Study Group. J Rheumatol 2001 May;28(5):1106-11.

(101) Ware JE Jr, Kosinski MA. Physical and mental summary scales:a manual for users of version 1. Lincoln (RI): Quality Metric Incorporated 2001.

(102) Loge JH, Kaasa S. Short form 36 (SF-36) health survey: normative data from the general Norwegian population. Scand J Soc Med 1998 Dec;26(4):250-8.

(103) Halvorsen H, Røksund O, Skadeberg B. Lungefunksjonstesting. 2009. Norsk barnelegeforening, Den Norske legeforening. Generell veileder. Ref Type: Online Source

(104) Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005 Aug;26(2):319-38.

(105) MacIntyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005 Oct;26(4):720-35.

(106) Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. Eur Respir J 2005 Sep;26(3):511-22.

(107) Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J 2005 Nov;26(5):948-68.

(108) Goutallier D, Postel JM, Gleyze P, Leguilloux P, Van DS. Influence of cuff muscle fatty degeneration on anatomic and functional outcomes after simple suture of full-thickness tears. J Shoulder Elbow Surg 2003 Nov;12(6):550-4.

(109) Williams MD, Ladermann A, Melis B, Barthelemy R, Walch G. Fatty infiltration of the supraspinatus: a reliability study. J Shoulder Elbow Surg 2009 Jul;18(4):581-7.

(110) Austin JH, Muller NL, Friedman PJ, Hansell DM, Naidich DP, Remy-Jardin M, et al. Glossary of terms for CT of the lungs: recommendations of the Nomenclature Committee of the Fleischner Society. Radiology 1996 Aug;200(2):327-31.

(111) Mayo JR, Aldrich J, Muller NL. Radiation exposure at chest CT: a statement of the Fleischner Society. Radiology 2003 Jul;228(1):15-21.

(112) Pachman LM, Abbott K, Sinacore JM, Amoruso L, Dyer A, Lipton R, et al. Duration of illness is an important variable for untreated children with juvenile dermatomyositis. J Pediatr 2006 Feb;148(2):247-53.

(113) Sato JO, Sallum AM, Ferriani VP, Marini R, Sacchetti SB, Okuda EM, et al. A Brazilian registry of juvenile dermatomyositis: onset features and classification of 189 cases. Clin Exp Rheumatol 2009 Nov;27(6):1031-8.

(114) Rider LG, Lachenbruch PA, Monroe JB, Ravelli A, Cabalar I, Feldman BM, et al. Damage extent and predictors in adult and juvenile dermatomyositis and polymyositis as determined with the myositis damage index. Arthritis Rheum 2009 Oct 29;60(11):3425-35.

(115) Ravelli A, Trail L, Ferrari C, Ruperto N, Pistorio A, Pilkington C, et al. Long-term outcome and prognostic factors of juvenile dermatomyositis: A multinational, multicenter study of 490 patients. Arthritis Care Res (Hoboken) 2010 Jan 15;62(1):63-72.

(116) Statistics Norway website, http://www.ssb.no/emner/03/01/royk/index.html. 2010. http://www.ssb.no/emner/03/01/royk/index.html. Ref Type: Online Source

(117) Tse S, Lubelsky S, Gordon M, Al Mayouf SM, Babyn PS, Laxer RM, et al. The arthritis of inflammatory childhood myositis syndromes. J Rheumatol 2001 Jan;28(1):192-7.

(118) Seshadri R, Feldman BM, Ilowite N, Cawkwell G, Pachman LM. The role of aggressive corticosteroid therapy in patients with juvenile dermatomyositis: a propensity score analysis. Arthritis Rheum 2008 Jul 15;59(7):989-95.

(119) Smith RL, Sundberg J, Shamiyah E, Dyer A, Pachman LM. Skin involvement in juvenile dermatomyositis is associated with loss of end row nailfold capillary loops. J Rheumatol 2004 Aug;31(8):1644-9.

(120) Stringer E, Singh-Grewal D, Feldman BM. Predicting the course of juvenile dermatomyositis: Significance of early clinical and laboratory features. Arthritis Rheum 2008 Oct 30;58(11):3585-92.

(121) Rider LG, Koziol D, Giannini EH, Jain MS, Smith MR, Whitney-Mahoney K, et al. Validation of manual muscle testing and a subset of eight muscles for adult and juvenile idiopathic inflammatory myopathies. Arthritis Care Res (Hoboken) 2010 Apr;62(4):465-72.

(122) Josefson A, Romanus E, Carlsson J. A functional index in myositis. J Rheumatol 1996 Aug;23(8):1380-4.

(123) Alexanderson H, Broman L, Tollback A, Josefson A, Lundberg IE, Stenstrom CH. Functional index-2: Validity and reliability of a disease-specific measure of impairment in patients with polymyositis and dermatomyositis. Arthritis Rheum 2006 Feb 15;55(1):114-22.

(124) Pachman LM, Hayford JR, Chung A, Daugherty CA, Pallansch MA, Fink CW, et al. Juvenile dermatomyositis at diagnosis: clinical characteristics of 79 children. J Rheumatol 1998 Jun;25(6):1198-204.

(125) Crowe WE, Bove KE, Levinson JE, Hilton PK. Clinical and pathogenetic implications of histopathology in childhood polydermatomyositis. Arthritis Rheum 1982 Feb;25(2):126-39.

(126) Wargula JC, Lovell DJ, Passo MH, Bove KE, Santangelo JD, Levinson JE. What more can we learn from muscle histopathology in children with dermatomyositis/polymyositis? Clin Exp Rheumatol 2006 May;24(3):333-43.

(127) Miles L, Bove KE, Lovell D, Wargula JC, Bukulmez H, Shao M, et al. Predictability of the clinical course of juvenile dermatomyositis based on initial muscle biopsy: A retrospective study of 72 patients. Arthritis Rheum 2007 Sep 28;57(7):1183-91.

(128) Gunawardena H, Wedderburn LR, North J, Betteridge Z, Dunphy J, Chinoy H, et al. Clinical associations of autoantibodies to a p155/140 kDa doublet protein in juvenile dermatomyositis. Rheumatology (Oxford) 2008 Jan 30.

(129) Bingham A, Mamyrova G, Rother KI, Oral E, Cochran E, Premkumar A, et al. Predictors of Acquired Lipodystrophy in Juvenile-Onset Dermatomyositis and a Gradient of Severity. Medicine (Baltimore) 2008 Mar;87(2):70-86.

(130) Gunawardena H, Wedderburn LR, Chinoy H, Betteridge ZE, North J, Ollier WE, et al. Autoantibodies to a 140-kd protein in juvenile dermatomyositis are associated with calcinosis. Arthritis Rheum 2009 May 28;60(6):1807-14.

I

II

III