Juvenile Dermatomyositis: Genetic Epidemiology and Disease Outcome

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Introduction and Overview

Although we have recently acquired a moderate amount of information concerning the clinical and laboratory features of the chronic inflammatory myopathies of childhood, there is a dearth of data concerning specific disease etiology and pathogenesis. The child and adult with chronic inflammatory myositis often share symptoms, but the toll taken by the particular disease and its therapies in the growing child must also be taken into account. In the past, biopsies of afflicted muscle were not frequently obtained as an aid in diagnosis. Recent study of biopsy material has yielded genetic and immunohistochemical information about the extent and diversity of alterations in muscle pathophysiology that allows the identification of unsuspected genetic disorders of muscle that provoke an inflammatory response. This information will aid in the further classification of children with the inflammatory myopathy syndromes into more homogeneous groups for effective diagnosis and therapy. Accurate measures of disease activity and chronicity are still needed to evaluate the success of therapeutic intervention. This discussion will review some of our current knowledge of the chronic inflammatory myopathies of childhood.

Clinical Manifestations

The onset of JDM is usually insidious, and follows an upper respiratory tract infection in over 50% of children (Table II). Constitutional symptoms of fatigue, low grade fever, weight loss and irritability are common at diagnosis. The characteristic rash usually appears first (often in sun exposed areas), usually followed within 3 months by proximal muscle weakness. Periorbital erythema, which may be heliotrope in color, edema and eyelid telangetasia occur in 50-90%. Small infarctions on the eyelids (especially the medial canthus) are not infrequent. The JDM rash can cross the nasal bridge, involve the upper torso, the extensor surfaces of the arms and legs, and the medial malleoli of the ankles, as well as the buttocks. Partial baldness can be a consequence of chronic scalp inflammation. The skin over the knuckles (MCPs, PIPs) is either hypertrophic or pale red, during active disease, may have a papular, “alligator skin” like appearance (Gottron’s papules) and evolve into colorless bands of atrophic skin. Extensive rash and a positive MRI may occur despite normal muscle-derived enzymes. Children with the amyopathic form of JDM (rash only) often develop myositis (and subsequent calcinosis) later in their disease course. Diffuse vasculopathy (nailbed telangectasia, infarction of oral epithelium and skin folds, or digital ulceration) is clearly associated with more severe disease, and may heal with either hyperpigmentation or vitiligo. A functional assessment of the disease activity (disease activity score, DAS) has been adopted by an international group of pediatric rheumatologists for use in the study of JDM (Table IV). The onset of proximal muscle weakness is often difficult to pinpoint, and is identified as difficulty in climbing stairs, combing hair, getting up from a siting position or rising unassisted from the floor without “climbing up the body” (Gower’s sign). The child is more quiet at play and cannot keep up with peers. On physical examination, there is neck flexor weakness (the inability to raise the head from the bed) or to perform

Table I. JUVENILE DERMATOMYOSITIS DIAGNOSTIC CRITERIA (Bohan and Peter)*

	JDM	PM
Characteristic rash	+	–
Symmetrical proximal muscle weakness	+	+
Elevated muscle derived enzymes	+	+
Muscle histopathology#	+	+
Electromyographic changes: inflammatory#	+	+
Exclusion of other rheumatic diseases	+	+

* (N Engl J Med 292:344, 1975)

= Diagnostic findings are dependent on selection of an involved site for testing. Muscle involvement in JDM is focal

Table II. 80 CHILDREN WITH JUVENILE DERMATOMYOSITIS: SYMPTOMS AT DIAGNOSIS*

SYMPTOM	n	(%)
RASH	80	(100%)
WEAKNESS	80	(100%)
MUSCLE PAIN	59	(74%)
FEVER	52	(65%)
DYSPHAGIA	36	(45%)
DIFFICULTY SPEAKING	35	(44%)
ABDOMINAL PAIN	30	(38%)
ARTHRITIS	29	(36%)
CALCIFICATIONS	18	(23%)
GI BLEEDING	11	(14%)

*Modified from J Rheumatol 1998

a sit up (weak abdominal); proximal muscles are often tender on compression.

Dysphagia, with penetration of the airway by fluids, is a very severe prognostic sign and prompts immediate aggresive medical intervention as well as administration of a soft diet (by nasogastric tube if needed) until a functional, protected airway returns. In rare cases, a respirator and tracheostomy are needed. Absorption of calories and medication may be impaired by gastrointestinal vasculitis, requiring intravenous administration of these agents. Complaints of constipation reflect decreased gastrointestinal smooth muscle function, while abdominal pain or diarrhea may indicate occult GI bleeding which can progress and be life threatening. Renal damage secondary to massive

Table III. 80 CHILDREN WITH NEW ONSET JDM: CRITERIA (Bohan and Peter) AT DIAGNOSIS

CRITERIA	NUMBER JDM TESTED	NUMBER (%) JDM	
		POSITIVE	NEGATIVE
RASH	80	80 (100%)	
PROXIMAL MUSCLE			
WEAKNESS	80	80 (100%)	
ANY ONE ABNORMAL MUSCLE ENZYME	80	72 (90%)	8 (10%)
Individual enzyme↑			
CPK↑	77	49 (64%)	28 (36%)
ALDOLASE↑	53	40 (75%)	13 (25%)
LDH↑	57	46 (81%)	11 (19%)
SGOT (ALT)↑	65	49 (75%)	16 (25%)
ELECTROMYOGRAM	44	36 (82%)	8 (18%)
MUSCLE BIOPSY * Muscle biopsy negative or non-diagnostic	52	42 (81%)	10 (19%)*

creatinine excretion can be averted by appropriate intravenous hydration. Cardiac involvement with conduction abnormalities is not uncommon, and, at onset, dilated cardiomyopathy may be observed.

Physical and occupational therapy provides passive stretching early in the disease course and, once active inflammation has resolved, provides direction for reconditioning muscles to regain strength and range of motion. Bed rest is not indicated except with some spinal cord compression fractures, and weight bearing helps osteopenia.

Loss of subcutaneous fat on the extremities, giving a hypermuscular appearance is seen in over one third of children with chronic symptoms of JDM. Weakened abdominal muscles with a “Pot belly” appearance, abnormal glucose and lipid metabolism consistent with partial lipodystrophy can be seen. Sterility may result if disease onset is before puberty. Children with antibody to the polymyositis/scleroderma (Pm/Scl) antigen often have bambooing of the digits, with loss of elasticity found in scleroderma. Thickened skin, cuticle overgrowth and range losses are indicators of a subset of refractory inflammatory myopathy more common in adults, which have severe lung involvement and are characterized by circulating antibody to the tRNA synthetases.

Other less common findings include hepatosplenomegaly (lymphadenopathy is frequent), ocular (retinitis, iritis), central nervous system (seizures) and evidence of renal impairment. Aspiration pneumonia may accompany unrecognized impairment in handling secretions and fluids. Another complication follows progressive bowel infarction with perforation and death. Depression and mood swings are part of the spectrum of CNS involvement and may be accentuated by steroid administration.

Calcinosis is present at diagnosis in over 20% of the JDM children, and this sequellae is associated with increased morbidity and mortality. The calcium deposits form in muscle, subcutaneous tissues and fascia, may drain a white cheesy material and resolve, or serve as a nidus for infection (most frequently staphylococcal), which can progress to septicemia.

TABLE IV JDM and DAS	**PRINTO** IRCCS S.Matteo Pediatria Generale e Reumatologia Piazzale Golgi 2, 27100 Pavia Italy **Tel +39-0382-50-20-25**

Patient Identification Number (Patient ID)
(ie Italy Paolo Rossi date of birth 25 March 1970 = **IT PR 250370)**

Visit Date (d/m/y)	Visit number	1

DISEASE ACTIVITY SCORE (DAS) with permission from Dr L. Pachman, USA

FUNCTIONAL STATUS (choose 1 category and report value in the score column; range for this section is 0 to 3):		Score
Normal function, able to attend school, keeps up with friends	0	
Mild limitations, tires after walking several blocks, general fatigue	1	
Moderate limitations, requires assistance with stair-climbing, activity of daily living	2	
Severe limits, wheelchair-bound, unable to attend school, climb stairs, etc.	3	

WEAKNESS (Score "1" point for each area of weakness noted; circle all that apply and sum all YES and then report total value in the score column; range score for this section 0 is to 8):

	No	Yes	
a) Neck flexor weakness	0	1	
b) Difficulty clearing scapula (abdominal weakness): can do sit-up with arms: 1) out 2) crossed 3) behind head 4) 1/3 cleared)	0	1	
c) Upper proximal muscle weakness	0	1	
d) Lower proximal muscle weakness	0	1	
e) Gower's sign (assisted/unassisted)	0	1	
f) Abnormal gait	0	1	
g) Difficulty swallowing	0	1	
h) Nasal speech	0	1	

SKIN INVOLVEMENT TYPE (choose one category and report value in the score column; range for this section is 0 to 4):

absent or resolved completely	0	
atrophic changes only	1	
erythema-mild	2	
erythema-moderate	3	
erythema-severe	4	

SKIN INVOLVEMENT DISTRIBUTION (choose one category and report value in the score column; range for this section is 0 to 3):

none	0	
focal (including area of joint-related skin)	1	
diffuse (including extensor surfaces of limbs shawl area)	2	
generalised (including trunk involvement)	3	

VASCULITIS If NONE of the categories below are present then score "0" point for this section, if ANY of the categories below are present, then score "1" point for this section; range is 0 to 1:

	Absent	Present	
a) Eyelid erythema	0	1	
b) Eyelid vessel dilation	0	1	
c) Eyelid thrombosis	0	1	
d) Nailfold erythema	0	1	
e) Nail bed telangiectasia	0	1	
f) Palate dilation	0	1	
g) Other	0	1	

GOTTRON'S PAPULES: If NO papules are present then score is "0" point, if any papules are present (mild, moderate or severe) then score is "1" point; range for this section is 0 to 1:

Absent	0	
Mild	1	
Moderate	2	
Severe	3	

SUM ALL THE VALUES IN THE SCORE COLUMN ON THE RIGHT SIDE TO OBTAIN THE DAS TOTAL SCORE (TOTAL RANGE MINIMUM 0 MAXIMUM 20):

DISEASE ACTIVITY SCORE (DAS) INSTRUCTIONS

A) NECK FLEXOR STRENGTH:

1. The examiner's hand is place on the child's forehead
2. The child is asked to lift her head from the examining table
3. The examiner's (who places the effort in the appropriate age range) evaluates the strength of the effort

B) SIT UP (DIFFICULTY CLEARING SCAPULA):

The child is asked to perform a sit up alone, without any counterbalance. Lack of age appropriate performance is counted as "weak" for the scoring. The gradations are as follows:

1. The child rolls to one side and needs to push off an elbow to sit up
   The child clears 1/3 or less of the scapula **COMMON PHYSICAL FINDINGS IN JDM**

   MUSCLE WEAKNESS:
   - Neck flexor weakness
   - Proximal muscles>distal

   RASH: Capillary changes
   - Eyelid margins
   - Soft palate
   - Nailfolds

GASTROINTESTINAL:
Weight loss (Constipation)
Dysphagia **COMMON PHYSICAL FINDINGS IN JDM**

MUSCLE WEAKNESS:
Neck flexor weakness
Proximal muscles>distal

RASH: Capillary changes
Eyelid margins
Soft palate
Nailfolds

GASTROINTESTINAL:
Weight loss (Constipation)
2. Dysphagia
3. Sit-ups are performed with: arms extended, crossed and behind head.

C) UPPER ARM STRENGTH:
1. The child sits on the examining table with the arms extended to the side at shoulder height and the examiner places the hands between the shoulder and the elbow and attempts to lower arms
2. The child holds the arm in front of body with elbows flexed, and the examiner attempts to extend the arm

D) LOWER ARM STRENGTH:
1. Child lies on back on the table and raises leg so that the foot is at least 18° from mattress
2. The examiner places hand midway between the hip and the knee and attempts to push the leg down on the mattress

E) GOWER'S SIGN:
The child sits on the floor (making sure that the examining gown is not in the way) and is asked to hold her hands at ear level and get up. Any unsteady manoeuvre or touching the body or the room's equipment (floor included) is noted and considered an "assisted"

F) ABNORMAL GAIT
Any deviation from normal gait is recorded as 1

G) DIFFICULTY SWALLOWING:
The child is asked if he had difficulty swallowing a cracker, and the answer is recorded

H) NASAL SPEECH:
The child is asked to say the alphabet up to the letter "E", and to say the letter "E" three times. The quality of speech is noted assigning 1 to any deviation from normal

DISEASE ACTIVITY SCORE (DAS) SCORING

To calculate the **TOTAL DAS SCORE** for a JDM patient it is necessary to add points for two components:
- Muscle weakness
- Skin involvement

	Muscle Weakness
1. Functional status	0-3 points possible
2. Weakness	0 or 1 point FOR EACH of the 8 categories; 8 total

RANGE POSSIBLE POINTS FOR MUSCLE WEAKNESS: 0 TO 11

	Skin involvement
3. Type	0-4 points
4. Distribution	0-3 points
5. Vasculitis	0 or 1 point, IF ANY are "present"
6. Gottron's papules	0 or 1 point, IF ANY is "present"

TOTAL POSSIBLE POINTS: RANGE 0 TO 9

To obtain the **TOTAL DAS SCORE** it is now sufficient to add the two components muscle weakness (range 0 to 11) and skin involvement (range 0 to 9).
THE POSSIBLE DAS TOTAL SCORE RANGE IS THEREFORE FROM 0 TO 20

Etiology

Several lines of evidence suggest that disease onset may be triggered by an infectious process in a genetically susceptible host. Children often have an antecedent illness in the three month period before the appearance of the first definite symptom of JDM (rash or weakness). Enterovirus (Coxsackievirus B) has been implicated both in the United Kingdom by RNA identification, and in the United States by rise in complement fixing and neutralizing antibody titers. However, neither viral RNA or bacterial DNA was identified in biopsied muscle of untreated newly diagnosed USA children who also did not have a rise in coxsackievirus titers. Another infectious candidate is group A betahemolytic streptococci. Case control studies of other potential candidates such as t.Gondii, HSV or Hepatitis B have shown that they are less likely to be a precipitating event.

Epidemiology

The average age of the child at the onset of JDM is 6 years. Children with their first JDM symptom under the age of 7 may have a milder course. In the USA, Caucasian JDM are more frequently reported, although children of African or Asian origin may be at increased risk for chronic myositis. The degree of female predominance varies worldwide, in the USA, the female:male ratio is 2.3 to 1. This genetic variation may alter disease susceptibility and expression. Multiple cases of myositis in a kindred are very rare, and familial autoimmune disease is not increased in JDM (as opposed to JRA).

Pathogenesis and Pathology

Disease susceptibility appears to be associated with at least one genetic marker: over 80% of USA children are positive for the HLA antigen DQA1*0501. Endothelial cell activation by presumed immune complexes with subsequent damage is associated with the release of von Willebrand factor antigen and deposition of immunoglobulin and terminal complement components. Proliferation of vascular smooth muscle results in occlusion of capillaries with subsequent capillary drop out and local infarction of tissue. The hallmarks of the histological diagnosis of JDM are occlusion of small vessels, perifascicular atrophy, a mononuclear cellular infiltrate. The perivascular mononuclear infiltrate is primarily composed of CD19+B cells, which may occur in clusters, but which are not activated. In early untreated disease (within 3 months of the first definite JDM symptom), there 4 times as many CD56+ NK cells in the muscle as in matched peripheral blood, suggesting that NK cells, which are major source of interferons (IFN), play an initial

role in the response to a presumed antigen. This line of reasoning is supported by preliminary analysis of gene expression profiles of untreated JDM muscle, compared with muscle from children with muscular dystrophy, showing increased IFN inducible genes. Other T cell subsets are found in muscle, but the number of monocytes/ macrophages (CD14+) are correlated with serum levels of neopterin, a macrophage derived T cell factor. Children with chronic inflammation will have increased fibrosis — mature collagen may replace damaged muscle fibers. With healing, regeneration of both new blood vessels and muscle fibers can be seen. Microscopic collections of calcium precipitate in areas of chronic inflammation. In affected skin, the epidermis is thinned, and the dermis demonstrates edema and vascular inflammation. On careful examination of the nailfold capillaries, in addition to areas of periungual avascularity with capillary drop out, vessel dilation can be seen, with characteristic terminal bush formation.

The disease course also appears to be associated with genetic factors. A change from G→A in the -308 promoter region of the TNFα allele is increased in children with JDM compared with control children and is associated with increased production of TNFα by circulating peripheral blood mononuclear cells as well as muscle fibers in the biopsy obtained before start of therapy. This polymorphism is also associated with a prolonged disease course, requiring immunosuppressive therapy for 36 months or more, and it is also associated with pathological calcifications.

Laboratory Findings

Serum elevation of any one of the muscle derived enzymes — creatine kinase (CK), aldolase, serum oxalic transaminase, and lactic acid dehydrogenase may reflect the degree of myositis, but early in the disease, muscle damage may be greater than these serologic markers indicate. An MRI (T2 weighted image with fat suppression) can localize the active site for muscle biopsy and/or EMG — about 20% of each are non-diagnostic if not directed by imaging. Antinuclear antibody (ANA, speckled pattern, unknown specificity) is present in > 60% of children (negative for SSA, SSB, Sm, RNP, DNA) and, initially, may be of high titer. Other myositis specific antibodies (rare in children) identify patients who have a difficult course; antibodies to Pm/Scl are most frequent. The ESR may be elevated or normal, anemia (Coombs negative) may be present; the rheumatoid factor is negative. Newer tests indicate immunological activity in JDM: despite the peripheral blood lymphopenia, active JDM have increased % CD19+ B cells which are highly associated with the disease activity score, as is von Willebrand factor antigen, released by damaged endothelial cells, and neopterin, released by activated macrophages. A rehabilitation cookie swallow can document significant palatorespiratory dysfunction with an unprotected airway. Muscle biopsy may provide evidence of disease activity/ chronicity not previously appreciated. Decreased bone density in both the lumbar Z score (age adjusted) as well as that of the radius is frequent in active disease and often accompanied by low osteocalcin and low vitamin D levels. Pathological calcifications can be detected by plain films, and occult blood, by stool test. Assessment of nailfold capillaries for loss of end row loops or bizarre “bush” formation is helpful in determining the severity of the systemic vasculopathy.

Treatment

Children who present with cutaneous findings only and no serologic or radiographic evidence of myositis may be treated initially with hydroxycloroquine (maximal dose of 5 mg/kg/day, if they do not have a history of color blindness) and oral steroids. However, they should be carefully monitored for the development of muscle involvement. Because osteopenia is a constant component of this disease, all our children are given 25-OH-Vitamin D at the dose appropriate for weight. Once muscle involvement has been documented, the intensity of immunosuppression is proportional to the severity of the immunological activation and muscle damage as assessed by function and histochemistry. For mild muscle damage, oral steroids may suffice at 1-2 mg/kg/day which may rapidly normalize the muscle enzymes, but leave the more resistant indicators of inflammation (% B cells, neopterin, vWF:Ag) still elevated, so that more intensive therapy is then required later in the disease course. For severe disease at onset, prompt institution of high dose intermittent intravenous methlyprednisolone (IVMP) therapy may be life saving, in conjunction with inhibitors of gastric acid secretion. Usually, the IVMP is given

at least three days in a rown; the frequency of subsequent drug administration is determined by the extent of tissue involvement as well as the patient's response and ranges from three times/ week to once a week until the laboratory indicators have normalized. Low dose oral prednisone (0.5 mg/kg) is given on non-IVMP days. Methotrexate (15 mg/M^2 or more, one time per week) is given in conjunction with folic acid (1 mg/day) if there is evidence of moderate vasculopathy and/or muscle fiber destruction. Cyclophos-phamide may be given with agents that protect the bladder when children with JDM who are non-responsive to IVMP and Methotrexate. The intensive immunosuppression may be result in decreased levels of IgG (below 200 mg%) and replacement IgG (0.4 gm/kg/month) may be required to prevent frequent infections. High dose intravenous Gammaglobulin may diminish the early symptoms, but it is not clear that the course of the disease is changed. Cyclosporin A has been successful in some resistant cases, in which the skin features predominate. A preliminary pilot study with Etanercept has not yet provided sufficient data to judge its efficacy.

Physical and occupational therapy provides passive stretching early in the disease course and, once active inflammation has resolved, provides direction for reconditioning muscles to regain strength and range of motion. Bed rest is not indicated except in special cases of spinal cord compression fractures, and weight bearing helps the osteoporosis.

In summary, this pediatric vasculopathy, JDM, appears to have genetic factors associated with both disease susceptibility as well as disease chronicity. There is epidemiological evidence of an antecedent illness before the first symptom of JDM, supported by both immunohistochemistry and gene expression profile data, that the child mounts a spectrum of interferon inducible genes in defense. The agent remains to be identified.

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