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JUVENILE DERMATOMYOSITIS

Clinical, laboratorial, histological, therapeutical and evolutive parameters of 35 patients

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ABSTRACT - This study was based on a prospective and a retrospective analysis of 35 patients who met Bohan and Peter criteria for juvenile dermatomyositis diagnosis.The mean follow-up time was three years ten months. Calcinosis was present in five (14.28 %) patients, cutaneous ulcers in four (11.42%), and systemic involvement in nine (27.71%) patients. All patients presented alterations in the serum levels of muscle enzymes, and all of them were submitted to muscle biopsy as a diagnostic procedure. Nine (25.71%) patients received corticotherapy prior to and 26 (74.28%) after the muscle biopsy. Chloroquine, methotrexate, cyclosporine, cyclophosphamide and intravenous immunoglobulin were used in patients with poor response to corticotherapy. Continuation of cutaneous manifestations was observed in 4 (11.43%) patients, laboratorial activity in 1 (2.85%), cutaneous and laboratorial activities in 3 (8.57%). Ten (28.57%) patients were out of activity, and 17 (48.57%) in remission at study end-point, on March 2002. Two (5.71%) patients died.

KEY WORDS: juvenile dermatomyositis, clinical findings, muscle biopsy, treatment, evolution, outcome.

Dermatomiosite juvenil: parâmetros clínicos, laboratoriais, histológicos, terapêuticos e evolutivos de 35 pacientes

RESUMO - Este estudo foi baseado na análise prospectiva e retrospectiva de 35 pacientes que preencheram os critérios diagnósticos de Bohan e Peter de dermatomiosite juvenil. O tempo médio de seguimento foi de 3 anos e 10 meses. Foi observado calcinose em 5 (14,28%) pacientes, úlcera cutânea em 4 (11,42%) e envolvimento sistêmico em 9 (22,71%). Todos os pacientes apresentavam alterações nos níveis séricos das enzimas musculares e todos foram submetidos a biópsia muscular como procedimento diagnóstico. Nove (25,71%) pacientes receberam corticoterapia antes e 26 (74,28%) depois da realização da biópsia muscular. Foram utilizados cloroquina, metotrexato, ciclosporina, ciclofosfamida e imunoglobulina endovenosa em todos os pacientes que não apresentaram boa resposta ao corticóide. Houve manutenção das manifestações cutâneas em 4 (11,43%) pacientes, atividade laboratorial em 1 (2,85%), atividades cutânea e laboratorial em 3 (8,57%). Dez (28,57%) pacientes estavam fora de atividade e 17 (48,57%) em remissão por ocasião do término do estudo em março de 2002. Dois (5,71%) pacientes faleceram.

PALAVRAS-CHAVE: dermatomiosite juvenil, achados clínicos, biópsia muscular, tratamento, evolução, prognóstico.

Dermatomyositis is a rare multisystem disease, whose etiology is unknown, characterized by a vasculitis that affects skin and muscles[1-3]. Most studies suggest that juvenile dermatomyositis (JDM) is autoimmune in pathogenesis and results from a vasculopathy. Both cell-mediate immunity to muscle antigens and immune-complex disease may play roles in pathogenesis[1]. Dermatomyositis is one of a heterogeneous group of acquired muscular diseases, an idiopathic inflammatory myositis marked by the presence of muscle weakness and histological evidence of inflammation in muscle biopsies. The characteri-

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zation of this group of diseases is based on muscular involvement, association of clinical manifestations, histological alterations, response to corticotherapy and prognosis[4,5].

Although clinical, laboratorial, histological, therapeutical and evolutive aspects of this disease have been analyzed in many previous studies, the majority of these studies were carried out some years ago, and therefore may not accurately reflect the status of the disease as it currently stands.

We describe clinical, laboratorial, therapeutical, histological and outcome parameters of 35 patients with JDM, based on a mean follow-up of 3 years 10 months, ranging from one year nine months to ten years three months.

METHOD

Patient selection: Thirty-five JDM patients fulfilling Bohan and Peter criteria[6], attending the Pediatric Rheumatology Unit at the Children's Institute of the University of São Paulo Medical School and Santa Casa de Misericórdia de São Paulo, have been studied. The evaluation was prospective from February/1999 to March/2002 in 25 patients, and retrospective over the period March/1991 to March/2002 in 10 patients. Bohan and Peter[6] suggested a classification based upon the presence or absence of five major criteria for diagnosis, including symmetric muscle weakness, evidence of inflammatory myositis in muscle biopsy, elevation of serum muscle enzymes, electromyographic evidence of inflammatory myopathy and dermatological pathognomonic features of dermatomyositis (heliotrope and Gottron´s papules). A diagnosis of JDM requires the presence of the pathognomonic rash and three of the other criteria[1]. A diagnosis of JDM is not excluded by the failure to meet one or more criteria[1].

Clinical evaluation: The clinical parameters analyzed were cutaneous manifestations such as heliotrope, Gottron papulae, erithema malar, palmar, periungueal, and in trunk, skin ulcers and calcinosis; involvement of internal organs, and muscle involvement according to the scale established by the Medical Research Council (MRC) in 1943[7] where: 0= no contractions, I= flicker or trace of contraction, II= active movement with gravity eliminated, III= active movement against gravity, IV= active movement against gravity and resistance, and V= normal power.

Laboratory evaluation: Antinuclear and anti-Jo-1 antibodies, erythrocyte sedimentation rate, serum levels of the muscle enzymes AST, ALT, DHL and CK were analyzed at the time of the biopsy.

Histopathological evaluation of skeletal muscle: Muscle biopsy specimens were obtained from brachial biceps muscle in all patients and a total of 37 muscle fragments were submitted to histopathological analysis. Specimens 2 and 5 were from a boy who presented persistent atypical cutaneous alteration and was resubmitted to muscle biopsy, with a 40-month interval from the first procedure. Additionally, specimens 9 and 14 were from a girl presenting an atypical association with mental retardation and who was submitted to a second biopsy for diagnostic confirmation after an 8-month interval. Muscle biopsy was performed before corticotherapy in 26 patients, and after the introduction of the medication in 9.

Routine standard histological and histochemical techniques were employed in muscle biopsies. Frozen sequential sections were stained with hematoxylin-eosin (H&E), modified Gomori trichrome, periodic acid Schiff, cytochrome C oxydase, NADH-tetrazolium-reductase, succinate dehydrogenase, adenosine triphosphatase pH 4.3 and 9.4, alkaline and acid phosphatase. Each biopsy specimen was coded and analyzed concomitantly by two investigators (AMES and SKNM). Presence of internal nuclei, focal myofibrillar loss, necrotic fiber, regenerating fiber, perivascular inflammation, endomysial inflammation, and increased connective tissue was observed in all preparations. Degenerative aspects were confirmed in acid phosphatase reaction, regenerative aspects in alkaline phosphatase and proliferation of connective tissue in modified Gomori staining. These alterations were analyzed semiquantitatively where: (-)= absent; (+)= present in less than 25% of the analyzed fields; (++)= present in 50%; (+++)= present in 75%; (++++)= present in 100%.

Therapeutical evaluation: All patients received corticotherapy (prednisone or metilprednisolone), and initial therapeutical response was analyzed at between 4 to 6 weeks following the introduction of medication; response was considered good, partial or bad, based on the improvement of muscle strength and/or cutaneous lesions. Chloroquine, methotrexate, cyclosporine, cyclophosphamide and/or intravenous immunoglobulin were administered to all patients that presented partial or bad initial responses.

Evolution analysis: Continuation of clinical activity was considered when there was persistent muscle weakness or cutaneous activity characterized by either the presence of erythema, heliotrope, Gottron papulae, cutaneous ulcers, or laboratorial activity during which, increased serum levels of muscle enzymes were maintained. Out of activity was deemed when there was an absence of symptoms and signs with continued medication and remissions when the children presented asymptomatic without medication. All patients were classified according to these different clinical criteria at study end-point, on March 2002.

RESULTS

Clinical characteristics: The mean age of disease onset was 6 years 10 months (± 3 years), median: 7 years 5 months, ranging from 1 year 5 months to 12 years 8 months. The gender distribution showed a predominance of females, being 2.8 females to 1

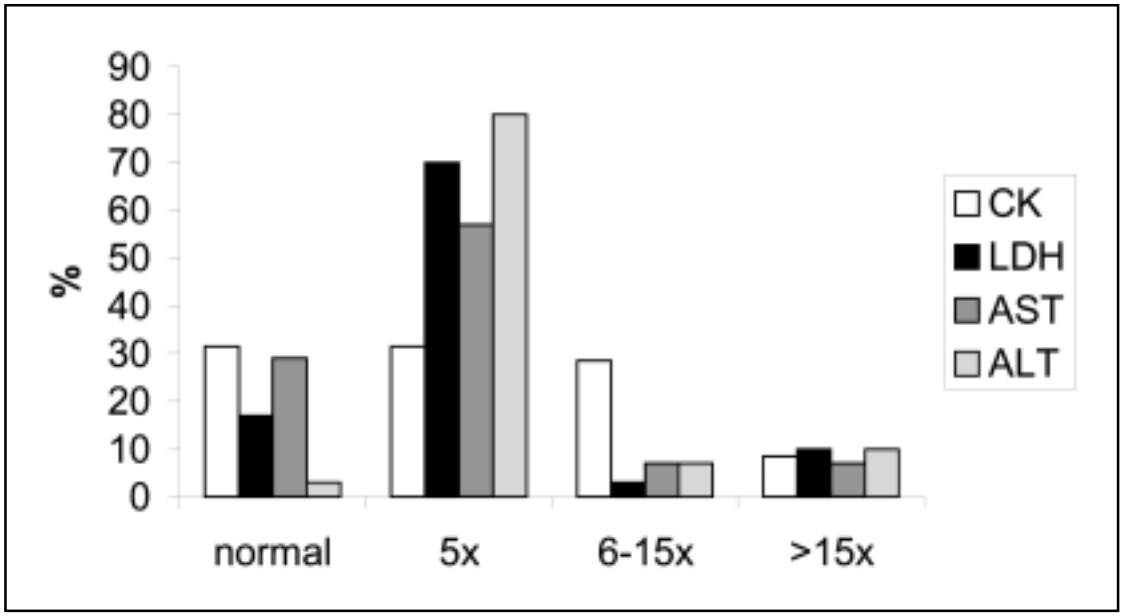
male (26 females and 9 males). All patients fulfilled Bohan and Peter criteria for dermatomyositis, with the presence of characteristic cutaneous lesion (Gottron´s papules and/or heliotrope), in addition to three other criteria. It was noteworthy that cutaneous and subcutaneous involvement was severe in four (11.42%), presenting cutaneous ulcer, while four other patients had calcinosis. Gastrointestinal tract involvement was observed in six (17.14%) patients, whereas five presented pulmonary involvement (14.28%), and three (8.57%) presented cardiac involvement. The majority of the patients presented some degree of muscle weakness, according to the MRC scale, with the exception of 3 patients (cases 2/5, 14 and 21) with normal muscle strength, in whom JDM diagnosis was established with the association of other signs (Table 1).

Laboratorial characteristics: The antinuclear antibody was positive in 14 (40%) patients, in contrast to the negativity of the anti-Jo-1 antibody in all patients, even in those presenting pulmonary involvement. The erythrocyte sedimentation rate was positive in five (14.28%) patients.

All patients presented at least one of the muscle serum enzyme altered. The serum levels of CK compared to serum levels of LDH, AST and ALT are shown in Graph 1. Interestingly, a normal range of CK was observed in 31.5%, in contrast to 3%, 17% and 29% of normal values for ALT, LDH and AST, respectively. A similar percentage of patients presented CK levels which were either normal, 5 times normal or up to 15 times normal, whereas a higher percentage of patients presented 5 times normal level of LDH, AST and ALT.

Histopathological findings for skeletal muscle (Table 1): Morphological alterations on muscle fibers including miofibrillar loss, necrotic fibers, regenerating fibers were observed in all cases except four (Fig 2). Degenerating aspects of muscle fibers were noted in all specimens and better demonstrated in acid phosphatase reaction (Fig 3).

The mean time up to the biopsy was 11 months (± 16 months 15 days) with median of 4 months, ranging from 1 to 64 months. Five patients had their biopsies performed more than one year after disease onset, including the two patients submitted to a second biopsy. Morphological alterations in muscle biopsies of these patients were markedly slight, ranging from absent, to 50% of the analyzed fields (+ +), in concordance to the moderate muscle weakness to normal muscle strength observed. Their CK levels were also normal, except in Case 9/14, which presented 25 times the normal level at first biopsy, decreasing to 3 times at the second biopsy performed 8 months later. It is noteworthy that in spite of the marked CK level increase in the latter case, the muscles' structural alterations, including muscle fiber morphological derangement and presence of inflammatory infiltration, were negligible. Moreover, the perifascicular atrophy was only demonstrated in the second biopsy. The two se-



Graph 1. Comparative serum levels of muscle enzymes (CK, LDH, AST, ALT). 5x = 5 times of normal value, 6-15x = 6 to 15 times of normal value, >15x = more than15 times of normal value.

Table 1. Clinical, laboratorial and skeletal muscule biopsy findings in 37 muscle specimens of 35 patients of juvenile dermatomyositis.

	Sex	Age at onset	Time up to biopsy (mo)	Signs & symptoms	Muscle strength	CK	Perifascicular atrophy	Focal myofibrillar loss	Necrotic fibers	Regenerating fibers	Perivascular inflammation	Endomysial inflammation	Increased connective tissue
1	F	6y3mo	1		II	711	P	+	+	++	++	+++	-
2	M	3y1mo	24	CCa	V	71	p	++	+	+	++	+	-
3	F	7y	2		IV	1785	p	++++	++++	++++	++	+	+
4	F	9y11mo	4	PG	I	1051	p	+++	++	++	++++	++++	+++
5	M	3y1mo	64	C	V	33	p	+	+	+	+	+	++
6	F	3y8mo	4		II	141	p	+++	++	++	+++	++	++
7	F	9y6mo	3	P	III	1281	p	++	+	+	+	+	+
8	M	8y8mo	24	C	IV	33	p	+	+	-	+	+	-
9	F	4y8mo	36		III	4365	p	-	-	-	+	-	+
10	M	1y6mo	4	UCCaG	II	240	p	+	+	-	+	+	+
11	F	5y6mo	4	UPG	IV	358	p	+	+	+	+	+	+
12	M	9y	18		III	197	p	+	+	+	++	++	+
13	F	5y8mo	3		IV	636	p	+	-	+	+	-	-
14	F	4y8mo	44		V	503	p	-	-	+	+	+	+
15	F	4y6mo	12		III	371	p	++	+	+	++	+	+
16	F	9y9mo	4		IV	57	p	-	-	-	+	-	-
17	M	7y8mo	1		III	2168	p	+++	+++	+++	+++	+++	-
18	F	1y5mo	12		III	2488	p	+++	+++	+++	+++	++	+
19	F	9y1mo	2	UPG	III	34	p	++	+	+	+	+	-
20	F	8y8mo	3		IV	5022	p	+	+	+	++	+	-
21	F	8y1mo	1		V	138	p	-	-	-	+	-	-
22	F	9y	4		III	1874	p	++	+	+	++	+	+
23	F	7y11mo	9	U	III	507	p	+++	++	+++	+++	+++	+
24	F	1y5mo	2		III	358	p	+++	++	+++	++	+	+
25	F	10y6mo	2	Ca	III	113	p	+++	+	+++	++	+	+
26	F	6y10mo	2	G	III	1173	p	-	-	-	-	-	-
27	F	8y	6		IV	734	p	-	+	+	+++	+++	-
28	F	5y8mo	4	PG	II	605	p	+	++	+++	+	++++	+
29	F	2y4mo	2		IV	2670	p	+	++	+++	+	+	+
30	M	11y	36	C	IV	88	p	+	-	-	+	-	-
31	M	8y6mo	1		II	1269	p	+	-	-	+	-	-
32	F	9y1mo	1		IV	1147	p	+	+	+	+	+	-
33	F	12y8mo	3		III	11640	p	++	++	++	++	++	+
34	M	7y	8		IV	504	p	++	-	+	++	+	-
35	F	13y	6		III	378	p	+++	+++	+++	+	+	-
36	F	6y	4		III	92	p	+++	+++	+++	+++	++	+
37	M	4y	3		IV	205	p	+	-	+	++	+	-

2 and 5 refer to same patient, as 9 and 14. F, female; M, male; mo, months; y, years; C, calcinosis; Ca, cardic; G, gastrointestinal; P, pulmonary, U, skin ulcer; p, present; (-), absent; (+), present in less than 25 % of the analyzed fiels; (++), present in 50%; (+++), present in 75%; (++++), present in 100%.

Table 2. Treatment administered to each of 35 JDM patients, initial response to corticotherapy, follow time and outcome at the study end-point.

Case	Corticotherapy		Initial response (4 -6w)	Chloroquine	Methotrexate	Cyclosporine	Cyclophosphamide	IV IgG	Follow up time (mo)	Outcome at study end-point
	before bx	after bx								
1		+	partial	+	+				77	out of activity
2		+	partial		+				130	laboratorial and cutaneous activity
3		+	good						72	remission
4	+		good						70	out of activity
5		+	partial		+				130	laboratorial and cutaneous activity
6		+	partial		+				58	remission
7		+	bad	+		+	+	+	56	out of activity
8		+	partial	+				+	102	remission
9		+	good						51	out of activity
10		+	partial	+	+	+			49	out of activity
11	+		bad	+	+	+	+	+	46	death
12		+	good						15	remission
13	+		partial	+					46	remission
14		+	good						51	out of activity
15	+		partial		+				41	out of activity
16		+	partial	+					38	remission
17		+	partial	+					39	remission
18		+	partial		+				39	out of activity
19		+	good						38	out of activity
20		+	good						38	laboratorial and cutaneous activity
21		+	good						36	cutaneous activity
22		+	no adherence						-	death
23		+	partial	+	+				35	cutaneous activity
24		+	partial		+				35	cutaneous activity
25		+	good						36	laboratorial activity
26		+	partial	+					33	remission
27	+		partial		+				29	remission
28		+	bad		+	+			30	out of activity
29	+		good						28	remission
30		+	partial	+					29	remission
31		+	good						39	remission
32		+	good						26	remission
33		+	partial	+					25	cutaneous activity
34	+		good						24	remission
35	+		good						22	remission
36	+		good						21	remission
37		+	good						21	remission

2 and 5 refer to same patient, as 9 and 14. Corticotherapy consisted on oral prednisone 1-2mg/Kg/day or intravenous methylprednisolone 30 mg/Kg/dose, Chloroquine 5-7 mg/Kg/day, methotrexate 0.8 –1.5 mg/Kg/week, cyclosporine 3-5 mg/Kg/day, cyclophosphamide 0.5 –1g/m^2/dose, IV IgG 2g/Kg/dose. bx, biopsy; w, weeks; IV IgG, intravenous Immunoglobulin; mo, months; +, medications administered to the patients.

quential biopsies performed in another case (2/5) with a 40-month time interval showed few differences between them. In the second biopsy, an increase in connective tissue and a slight decrease in perivascular inflammation, which had been scant from the outset, were observed.

30 biopsies were performed on patients during their first 12 months of symptoms, and among them 5 biopsies were carried out in the first month, 6 in the second month, 5 in the third month, 8 in the fourth month, 2 in the sixth month and 4 between the seventh and twelfth months of disease onset. Although the number of cases in each time interval was too small to permit statistical analysis, the muscle lesion and inflammatory infiltration were more evident in the group with less than one year of disease. 40% of biopsies performed in the first month presented muscle alteration for more than 50% (++) of fields studied, whereas the frequency of muscle lesions increased to 67% - 100% of cases in subsequent time intervals up to 12 months.

Perifascicular atrophy was detected in all cases, independent of evolution time, being present even in the first month of the disease (Fig 1). Interestingly, slight proliferation of connective tissue was observed even in the first month since the onset of symptoms.

Surprisingly, striking inflammatory infiltration (++/+++/++++), either endomysial or perivascular, was observed in 5 out of 9 patients who had been treated with corticotherapy before the biopsy procedure. Coincidentally, the great majority (4/5) were female patients.

No relation was observed between degree of morphological muscle lesion, degree of inflammatory infiltration and CK serum level. Similarly, no association was found concerning CK level and evolution time interval up to biopsy and degree of muscle weakness.

Therapeutical and evolutional characteristics: All patients received corticotherapy, 9 (25.71%) patients received therapy prior to muscle biopsy, and 26 (74.28%) patients after it. 15 patients presented initial good response needing no complementary therapy. Partial response was observed in 16 patients, and bad response in 3, whom received additional associated therapy with Chloroquine (12 patients), Methotrexate (12), Cyclosporine (4), Cyclophosphamide (2) and intravenous Immunoglobulin (3). The medication administered to each patient, along with corresponding initial therapeutical status and outcomes at study end-point (March 2002), are listed in Tables 2 and 3.

Nine patients out of 19 (47%) with partial or bad response, presented systemic involvement, in contrast to 20% involvement for those presenting good response (3/15). Additionally, patients with worse responses presented worse muscle weakness at the time of biopsy, as 62% of patients with an unsatisfactory response had grade I-III muscle strength, whereas similar muscle degree was observed in 46% of patients with good response.

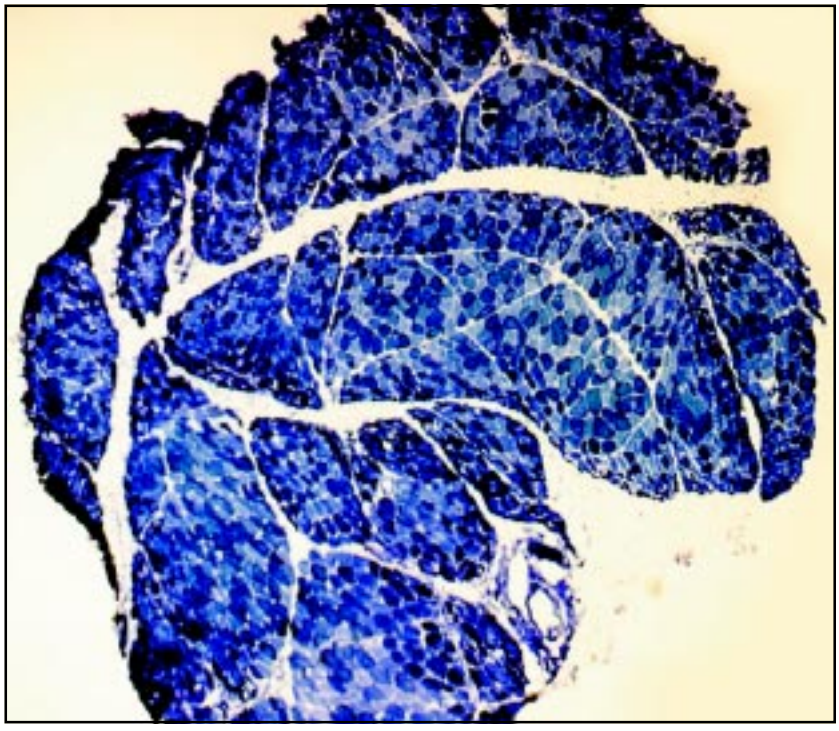


Fig 1. Transversal section of frozen skeletal muscle, 5μ of thickness, histochemical preparation of NADH, 40x. All the fascicles in the fragment show perifascicular atrophy characterized by muscle fibers with decreased diameter distributed at periphery of the fascicle.

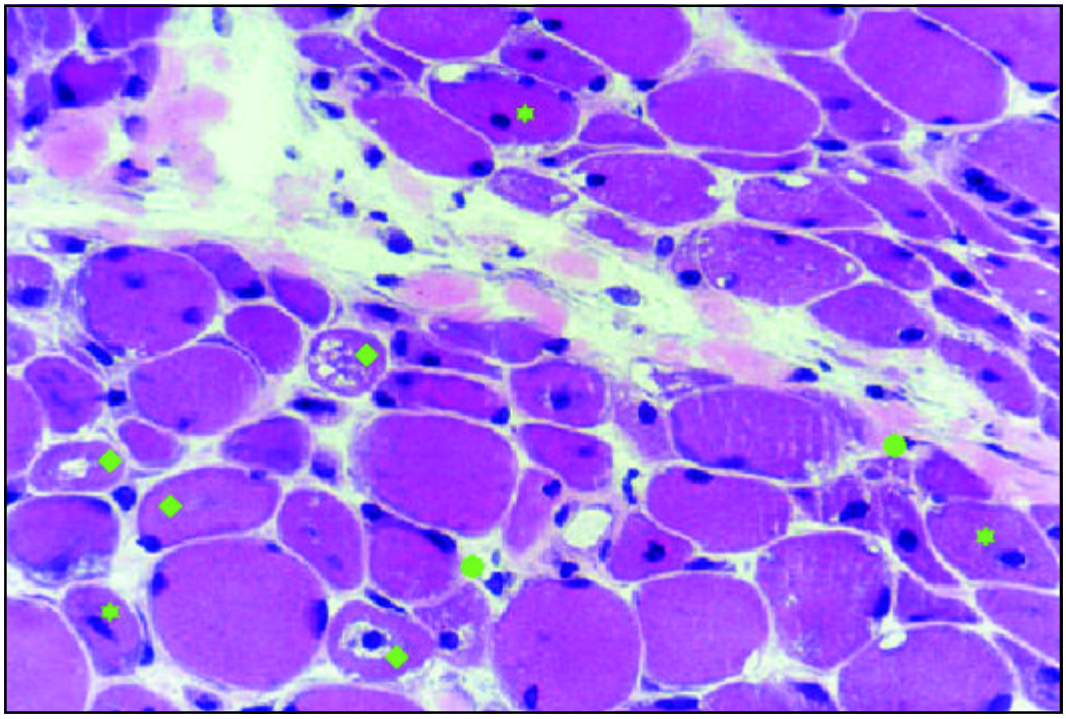


Fig 2. Transversal section of frozen skeletal muscle, 5m of thickness, histological preparation of hematoxilin-eosin, 400x. Note the marked morphological alterations in the majority of muscle fibers characterized by the presence of internal nuclei ( ), focal myofibrillar losses with vacuolization ( ) and necrotic fibers ( ).

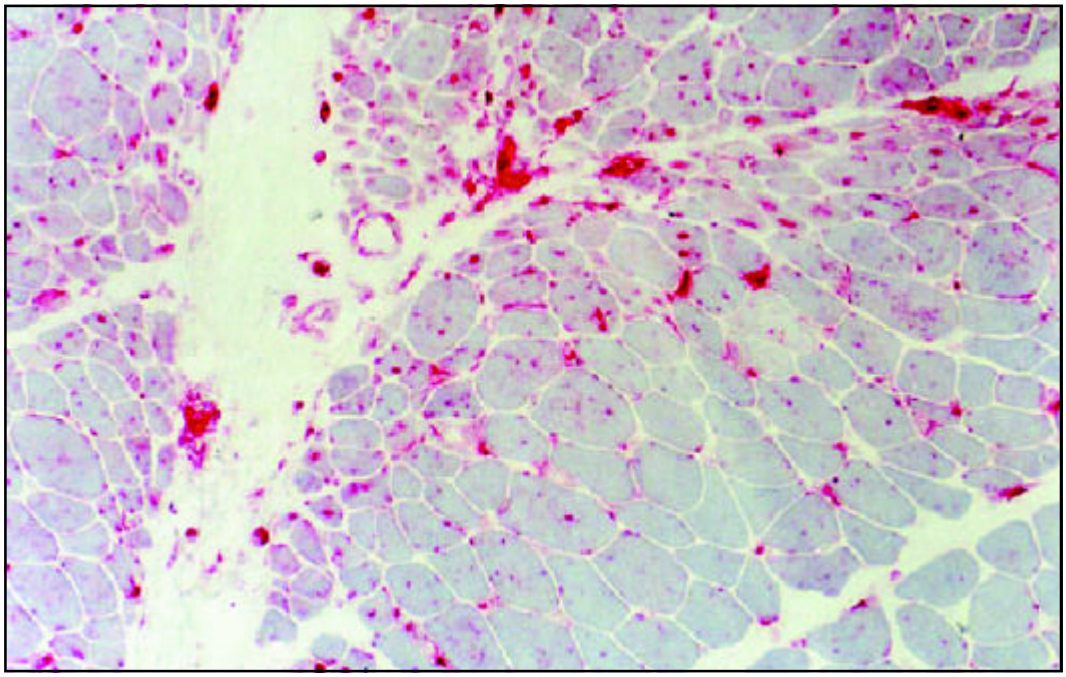


Fig 3. Transversal section of frozen skeletal muscle, 5m of thickness, histochemical preparation of acid phosphatase, 200x. Red reaction in muscle fibers and vessels represent lisossomal activity distributed mainly at the periphery of fascicles.

The analysis of outcomes at study end-point revealed continuation of clinical activity associated to cutaneous manifestations in 4 (11.43%) patients, laboratorial activity in 1 (2.85%), cutaneous and laboratorial activities in 3 (8.57%), out of activity in 10 (28.57%), and remission in 17 (48.57%) patients. Two (5.71%) patients died: one with a complication of multisystemic involvement and another due to non-adherence to the treatment. 30% of female patients (8/26) presented unsatisfactory evolution, in contrast to 11% of male patients (1/9).

Table 3. Therapeutical response in 35 JDM patients.

	Corticosteroids	Chloroquine	Methotrexate	Cyclosporine	Cyclophosphamide	IV IgG
Good response	15	9	6	3	1	1
Partial response	16	2	5	-	-	1
Bad response	3	1	1	1	1	1
No adherence	1					
Total of patients	35	12	12	4	2	3

IV IgG, intravenous Immunoglobulin G.

No relapses were observed among patients in remission, follow-up being for 37 months on average. 11 out of 17 patients in remission had more than 2 years of follow-up.

Among 13 patients presenting systemic involvement, 8 patients (61.5%) presented good outcomes, independent of the CK level, degree of muscle strength or inflammatory infiltration in muscle biopsy.

DISCUSSION

JDM makes up approximately *5%* of annual visits to Pediatric Rheumatology reference centers[4]. In our experience, JDM ranks fourth among rheumatologic diseases, after rheumatic fever, juvenile rheumatoid arthritis and systemic lupus erythematosus[8]. It has been estimated that about one third of the 1000 or so cases published in the world literature, were in the pediatric age group (under 16 years)[9].

JDM is different from the adult form of dermatomyositis. The clinical presentation in children is more frequently insidious and may be dominated by constitutional symptoms of fatigue, malaise, fever, anorexia and weight loss. Additionally, children have more often a multisystem vasculitis, which may involve the skin, gastrointestinal mucosa, heart, and retina. Children with longstanding, untreated disease, with generalized cutaneous vasculitis, frequently develop calcinosis. The association of malignancy with the development of myositis has been well described in adults, but only rarely reported in children . Once remission is achieved, children appear to return to normal muscle strength and function, more frequently than adults with dermatomyositis[10-12].

Outcome depends on the precocity of diagnosis and treatment. Predictive parameters to guide the correct therapeutical approach, and for prognosis, are still lacking in JDM.

Therefore, this study was designed to describe clinical, laboratorial, and histological findings, and to correlate them to early response to the therapy adopted and to longstanding outcome features, in *35* JDM patients.

Age and gender distribution: It was previously reported that the most common age for onset of JDM was 6 years for boys, with two peaks of 6 years and 10 years for girls, with an overall average of 7 years for disease onset[1]. The mean age of disease onset in our study was in accordance with these reports, being 6 years 10 months on average, 6 years for boys, with peaks of 4 years 10 months and 9 years 6 months for girls.

A female predominance has been described in most of the rheumatic diseases in childhood, as was observed in the present study with a female to male proportion of 2.8:1.

Clinical findings: All patients in this study fulfilled these diagnostic criteria. An association with widespread vasculitis has also been made in this childhood disease. In fact, 34% of our patients presented systemic involvement including gastrointestinal tract, cardiac, respiratory and more severe cutaneous alterations, than predicted within the diagnostic criteria.

JDM may be associated with motor dysfunction of the entire gastrointestinal tract. Abnormal esophageal motor function is a complication of the disease and esophageal symptoms are frequently present. Small and large bowel involvement has also been documented[13]. Our patients presented esophageal gastric reflux, dysphagia and upper digestive tract bleeding.

There are few reports in the literature on cardiac involvement in JDM[1]. A few patients have cardiac murmurs or pericardial friction rubs and a high proportion show ECG changes[14]. In this study, three patients presented tachicardia with hypercinetic circulatory state shown by electrocardiogram.

Lungs may be affected in JDM, primarily or through complications of muscle weakness[15]. In this study, aspirative pneumonia was present in two patients and interstitial disease in three patients. The pathological mechanisms of interstitial lung disease remain unknown. There is evidence that both cell mediated and humoral immunity play a role in the pathogenesis of this lesion. More recently, the role of the anti-Jo-I antibody has been highlighted[15] in association with pulmonary interstitial disease. However, the anti-Jo-I antibody was negative in all patients in this study, even in those patients with interstitial disease, which corroborates previous reports describing the rarity of its presence in childhood.

Dystrophic calcification is two or three times more frequent in JDM than in adult dermatomyositis, occurring in 40% to 75% of children with JDM[16]. The calcification occurs in the interstitial of muscle or in the subcutaneous tissue, and it is readily visible on X-ray. Nodules of calcium may be extruded through perforations in the skin. We found a lesser incidence of calcinosis in our casuistic (11%) than seen previously.

Skin ulceration may be considered among the systemic angiopathy referred to by Banker and Victor[17], where necrotizing vasculitis has been identified. The same pathological condition has been described in skeletal muscle, subcutaneous tissue and gastrointestinal tract, resulting in muscle infarction, gastrointestinal ulceration, bleeding and perforation, constituting one of the major causes of death[18]. Few patients in the present study presented skin ulceration (11%), however it was present in one of the 2 fatal cases, being part of the systemic angiopathy that lead to death.

Although muscle weakness is one of the criteria for diagnosis of inflammatory myopathy, it is not easy to assess this alteration objectively. The strength of muscles may be graded according to their ability to act against gravity and resistance offered by an examiner, as proposed by the well-known MRC grading system. However, such a system has the disadvantage of being subjective, depending on examiner impression. Moreover, about 40% of extremity muscles such as rotators and muscles moving fingers and toes, are not significantly affected by gravity. A careful examination of muscle strength, taking into account these difficulties, depicted only three patients with normal muscle power from our cases. A better, non-invasive method of assessing muscle function is necessary to permit correlation of this parameter to other findings, thus permitting a better search for predictive factors of evolution in JDM[19].

Laboratorial and histopathological findings of skeletal muscle: It has been stressed that the serum levels of muscle enzymes are important for diagnosis and for monitoring the effectiveness of therapy[1]. However, CK levels were normal in 31% of our patients, in spite of presenting muscle weakness and/or structural alterations and inflammatory infiltration in muscle biopsy. Unfortunately, the degree of increase in CK level did not also predict the outcome. The other muscle enzymes presented similar behavior.

Other serum specific markers for myositis have been considered, and antibody anti-Mi-2, an antibody against cytoplasmic ribonucleoprotein evolved in the translation process, is one of these candidates. However, in contrast to presence of anti-Mi-2 of up to 95% in dermatomyositis with classical cutaneous involvement, only 10-50% of cases of JDM presented this antibody. Therefore, most previous studies do not recommend routine clinical testing for anti-Mi-2 since the yield is likely to be low. Moreover, it seems not to be a prognostic factor[20].

Other non-specific indicators of inflammation, such as erythrocyte sedimentation rate, tend to correlate with the degree of clinical inflammation, and have are useful in differentiating inflammatory myopathies from non-inflammatory muscle disorders. However, the reported results are also variable and likely to be low.

On the other hand, muscle biopsy is important for establishing the diagnosis of an inflammatory myopathy and for understanding the character of the inflammatory change, such as its distribution and the degree of parenchyma involvement[21]. Although perifascicular atrophy may be present in other pathologies as dystrophies, it was described as a frequent finding in definite DEM[22] and was found in all cases studied here (Fig 1). Perifascicular atrophy in the present study was observed as early as 1 month from the onset of symptoms and persisted for at least 64 months of the active disease. The inflammatory infiltration seems to be more evident from between two months of disease onset and up to one year, mostly in the first six months of the disease. After one year, there is apparently a decrease in the inflammatory alterations, even if untreated.

The introduction of corticotherapy tends to clear the inflammatory infiltration in lesioned tissues, but 5 of our treated patients presented inflammatory cells in muscle tissue and yet had good outcomes. However, the question as to whether the inflammatory reaction would have been greater without the treatment remains.

Despite muscle biopsy being a fundamental diagnostic tool, its histological analysis is insufficient as a prognostic factor. Future biological markers, such as proteins involved in the pathomechanisms of tissue lesions, may be studied in muscle specimens by immunohistochemical methods to guide the best therapeutical approach[23-25].

Therapeutical and evolutional characteristics: Treatment with corticosteroids does improve the prognosis. The death rate is reduced from around 33% to less than 10%[26]. The acute stage, during which therapy is required, is generally self-limited and lasts for about two years[27]. Chloroquine has been used as a steroid-sparing agent, and as a drug that is effective in treating the dermatitis of JDM[1]. Glucocorticoid resistance or dependence is the primary indication for the use of immunosupressive drugs[1]. It is difficult to evaluate the efficacy of these drugs, since there have been no controlled trials in JDM treatment. However, some publications confirm the efficacy of corticotherapy, or other highly selective immunosuppressive therapy, in the management of this disease during its acute phase. Most authors agree that early diagnosis and early aggressive therapy, result either in reducing mortality or improving functional recovery[28]. Thus, the 74% remission or out of activity achieved by our patients at the study end-point, also corroborates these reports. The high incidence (88%) of some extent of response to corticotherapy in our study, also confirms the efficacy of its use, and strongly suggests this as the drug of first choice.

The majority of fatalities occur within two years of disease onset, according to several reports[29], although there are several periods of increased vulnerability to life-threatening complications, during the initial year of treatment. Gastrointestinal ulceration, hemorrhage and perforation, and myocardial and respiratory failure have been described as major causes of death in JDM[30]. Pulmonary involvement is another important cause of morbidity and mortality in JDM. Concordantly, one of our cases presented a fatal evolution owing to complications of multisystemic involvement. Non-adherence to treatment was the cause of our other fatal case. Later relapses with corticosteroid treatment programs (prednisone doses < 15 mg) in the first 24 months after cessation of treatment have also been described[31]. Our patients in remission, observed for more than 2 years on average, have not presented relapses to date. A lengthier follow-up will permit further conclusions to be drawn on the outcomes.

The present analysis of a representative number of cases of JDM, a rare childhood multisystemic disease, permitted us to conclude that:

1. Skeletal muscle involvement can be assessed by clinical evaluation, a qualitative method; by CK serum levels, not always corresponding to clinical or structural muscle condition; and by muscle biopsy, with perifascicular atrophy as a constant finding.
2. Adequate diagnosis and therapy resulted in a 74% good outcome within a mean follow-up period of 3 years 10 months.
3. None of the parameters analyzed, including muscle weakness, multisystemic alteration, CK level, degree of inflammatory infiltration and muscle fiber morphological alteration, presented predictive value.
4. Further studies are necessary aimed at finding biological markers to select and guide new therapeutical approaches for those patients presenting drawbacks.

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