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## Risk factors associated with calcinosis of juvenile dermatomyositis

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### Abstract

**Objective:** To identify risk factors associated with calcinosis in children and adolescents with juvenile dermatomyositis.

**Methods:** A review was carried out of the medical records of 54 patients with juvenile dermatomyositis. Data were collected on demographic characteristics, clinical features: muscle strength (stages I to V of the Medical Research Council scale), pulmonary involvement (restrictive pulmonary disease with presence or absence of anti-Jo1 antibodies), gastrointestinal problems (gastroesophageal reflux) and/or heart disease (pericarditis and/or myocarditis); laboratory tests: elevated muscle enzyme levels in serum (creatine phosphokinase, aspartate aminotransferase, alanine aminotransferase and/or lactate dehydrogenase); and on the treatments given: corticoid therapy in isolation or associated with hydroxychloroquine and/or immunosuppressants. The patients were divided into two groups, depending on presence or absence of calcinosis and data were evaluated by both univariate and multivariate analyses.

**Results:** Calcinosis was identified in 23 (43%) patients, and in six (26%) patients it had emerged prior to diagnosis while in 17 (74%) it was post diagnosis. The univariate analysis revealed that cardiac ( $p = 0.01$ ) and pulmonary ( $p = 0.02$ ) involvement and the need for one or more immunosuppressor (methotrexate, cyclosporine A and/or pulse therapy with intravenous cyclophosphamide) to treat juvenile dermatomyositis ( $p = 0.03$ ) were all associated with an increased incidence of calcinosis. The multivariate analysis then demonstrated that only cardiac involvement (OR = 15.56; 95%CI 1.59-152.2) and the use of one or more immunosuppressor (OR = 4.01; 95%CI 1.08-14.87) were independently associated with the presence of calcinosis.

**Conclusions:** Calcinosis was a frequent development among these juvenile dermatomyositis cases, generally emerging as the disease progressed. Calcinosis was associated with the more severe cases that also had cardiac involvement and where immunosuppressors had to be included in the treatment.

*J Pediatr (Rio J). 2008;84(1):68-74: Juvenile dermatomyositis, calcinosis, risk factors, heart, lungs, immunosuppressors.*

### Introduction

Juvenile dermatomyositis (JDM) is a multisystemic disease of unknown etiology, which is characterized by vasculitis primarily affecting the skin and muscles.<sup>1-3</sup> It is part of a

heterogenous group of acquired muscle diseases, the idiopathic inflammatory myopathies, whose common denominator is the presence of weak muscles with inflammatory infiltrates. Characterization of this group of pathologies is

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based on its pattern of muscle involvement, the presence of associated clinical manifestations, histopathological findings, response to treatment and prognosis.<sup>4-6</sup>

This is a rare disease that predominantly affects females, at a proportion of 2:1, and which has an incidence of 3.2/1,000,000 children and adolescents/year in the United States.<sup>7</sup> Despite its rarity, it is the fourth most frequent disease at tertiary pediatric rheumatology services, and there are no Brazilian studies of its epidemiology.<sup>8</sup>

The initial phase of the disease is characterized by vasculitis<sup>9</sup> and, later, calcinosis or dystrophic calcifications may appear.<sup>1</sup> These are calcium deposits that appear in muscle or subcutaneous tissues. Patients with calcinosis have normal levels of calcium and phosphorous in serum, in contrast with metastatic calcifications (which are observed with hyperparathyroidism), when these metabolites are at elevated levels.<sup>10</sup>

Calcinosis are more common in the pediatric age group, affecting from 10 to 70% of children and adolescents with JDM, compared with 30% of adults with dermatomyositis (DM).<sup>8,11,12</sup> The etiopathogenesis of calcinosis is unknown. It is believed that calcium salt deposits occur with severe cases of the disease with persistent inflammation<sup>13</sup> (generalized cutaneous vasculitis, muscle weakness and sustained muscle enzyme levels in elevation) and which do not respond to corticoid therapy.<sup>8,10,12-16</sup> However, the majority of publications are just case reports.

There is just a single study of 35 cases that has investigated the risk factors associated with calcinosis in patients with JDM, with univariate and multivariate analysis models.<sup>17</sup> The rarity of research into calcinosis in JDM and the significant number of patients with this disease at our service prompted us to carry out this study.

Our objective was, therefore, to investigate risk factors (demographic data, initial and progressive clinical manifestations, laboratory tests and treatment) associated with calcinosis in children and adolescents with JDM.

## Methods

This was a cross-sectional study. A total of 54 children and adolescents were studied, enrolled from those treated at the Pediatric Rheumatology Unit of the Instituto da Criança, Hospital das Clínicas, Universidade de São Paulo Medical Faculty (ICr-HC-FMUSP) with diagnoses of JDM. These patients were followed from January 1987 to December 2003. Their definitive diagnoses of JDM were established according to criteria laid out by Bohan & Peter, and recommended by the American College of Rheumatology,<sup>9</sup> and based on the presence of characteristic erythema associated with three of the four criteria listed in Table 1.

Patients were only enrolled if all of the data described were on their medical records. These patients were followed for a minimum period of 6 months and a maximum of 16 years (mean follow-up period of 5.4 years and median of 6.7 years).

The analysis was retrospective and carried out by means of completing a protocol that covered patients' clinical, laboratory and treatment characteristics. The protocols were then divided into two groups, depending in the presence or absence of calcinosis.

Calcinosis was diagnosed based on the presence of calcium deposits that were palpable on physical examination and/or deposits visible on X-rays of soft tissues and involving the trunk, abdomen, upper and/or lower limbs. These were then classified into four subtypes: calcinosis cutis circumscripta (superficial plaques or nodules confined to the skin or subcutaneous tissue), calcinosis tumoral or *universalis* (large deposits that may extend to deeper tissues, including muscles), calcinosis along the muscular fascia and tendons and extensive calcium deposits all over the surface of the body.<sup>18</sup> All cases had normal levels of calcium and phosphorous in serum.

The two groups were compared in terms of the following characteristics: demographic data (sex, age at disease onset, time between onset of the disease and start of treatment) and

**Table 1** - Bohan & Peter's criteria for the diagnosis of juvenile dermatomyositis

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Cutaneous involvement: violaceous discoloration and edema around the eyes (the heliotrope sign) and/or erythematous scaly papules on the eruption on the knuckles (the Gottron rash)
Symmetrical, muscle weakness at the waist, pelvis and anterior neck flexor muscles, with or without dysphagia and involvement of the respiratory musculature
Elevated muscle enzyme levels, particularly creatine phosphokinase, and frequently aldolase, aspartate aminotransferase, aspartate alanine transferase and lactate dehydrogenase
Electromyography findings show short motor units, polyphase waves, fibrillations, positive waves, insertional irritability, high frequency and repetitive discharges
Muscle biopsy shows evidence of inflammatory myopathy: necrosis of type I and II muscle fibers, phagocytosis, degeneration and regeneration of muscle fibers with variable fiber caliber, interstitial mononuclear cells, endomysial cells, perimysial cells or perivascular cells

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degree of muscle strength at diagnosis (waist, pelvis and anterior neck flexors, according to Medical Research Council criteria. The latter classification consists of the following stages: 0 (no contraction), 1 (minimal contraction), 2 (active movement in the absence of gravity), 3 (movement against gravity), 4 (movement against gravity and resistance) and 5 (normal strength).<sup>19</sup> Comparisons were also made based on elevated levels of one or more muscle enzymes (any figure above the upper limit of normality): creatine phosphokinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH). The following characteristics observed during follow-up were also analyzed: pulmonary involvement (presence of restrictive disorders on pulmonary function test and/or interstitial abnormalities on thin slice computerized tomography, with anti-Jo-1 antibody assay), gastrointestinal symptoms (gastroesophageal reflux, assessed by contrastive X-rays of the esophagus, stomach and duodenum and/or pH-metry) and cardiac involvement (pericarditis and/or myocarditis, detected using echocardiogram with Doppler), deaths and their causes and treatment.

All patients were initially treated with prednisone (1 to 2 mg/kg/day) or pulse therapy with methylprednisolone (30 mg/kg/dose for 3 consecutive days). Those who did not respond or who responded partially to corticoid therapy (continued muscle weakness and/or cutaneous activity), were given an antimalarial in association (chloroquine diphosphate or hydroxychloroquine sulphate), immunosuppressors (methotrexate, cyclosporine A and/or pulse therapy with intravenous cyclophosphamide) and/or intravenous gammaglobulin.

This study was approved by the Research Ethics Committee at the HC-FMUSP, and the patients and/or their parents or guardians signed free and informed consent forms.

Univariate statistical analysis was performed using Fisher's exact test and the chi-square test to compare demographic data, and clinical, laboratory and treatment characteristics between the two study groups: with and without calcinosis. Student's *t* test for unpaired samples was used to compare mean age at disease onset for the two groups. The multivariate analysis employed backward stepwise logistic regression. Those independent variables that exhibited a level of statistical significance  $\leq 5\%$  were chosen for the multivariate analysis model. The level of significance was set at 5% for all tests.

## Results

The principal clinical, laboratory and treatment characteristics of the 54 JDM patients are given in Table 2.

Clinical and/or radiographic calcinosis was present in 23 (43%) patients, 15 (65%) females and eight (35%) males. This had already appeared before JDM was diagnosed in six (26%) cases, and in one of these it was the initial manifestation of the disease. In these cases, the median time between calcinosis and diagnosis of JDM was 9 months (variation of 15 days to 2 years). The deposits appeared after diagnosis in 17 (74%) patients. Calcinosis were predominantly located in the soft tissues of upper limbs, observed in 18 (78%) patients; followed by lower limbs in 13 (56.5%); the trunk in three (13%); scrotal and testicular region in two (8.7%) and urethral area in one (4.3%). Calcinosis circumscripta affected 15 (65%) patients, three had calcinosis universalis (13%) and there were extensive calcium deposits all over the surface of the bodies of five patients (22%).

Calcinosis was associated with persistent ulcerations in four (17%) patients, with recurrent secondary infections with

**Table 2** - Clinical, laboratory and treatment characteristics of 54 patients with juvenile dermatomyositis

Variables	n = 54 (%)
Female sex	40 (74)
Muscle strength levels I, II or III	27 (50)
Muscle strength level IV	27 (50)
↑ CK	25 (46)
↑ AST	38 (70)
↑ ALT	32 (59)
↑ LDH	46 (85)
Pulmonary involvement	15 (27)
Cardiac involvement	8 (15)
Gastrointestinal involvement	22 (40)
Treated with prednisone	54 (100)
Treated with one or more immunosuppressor	25 (46)

ALT = aspartate alanine transferase; AST = aspartate aminotransferase; CK = creatine phosphokinase; LDH = lactate dehydrogenase.

pododermatitis or abscesses in five cases (22%) and with articular contractures in five (22%). Calcium was liberated in a form similar to "chalk-powder" in three (13%) cases.

The initial treatment given to the patients with calcinosis to control their JDM was corticosteroids (prednisone and/or pulse therapy with methylprednisolone) in all cases. It proved necessary to add chloroquine diphosphate or hydroxychloroquine sulphate in four (17.3%) cases and one or more immunosuppressor was prescribed for 16 (69.5%): methotrexate in eight cases (34.7%), cyclosporine A in seven (30%) and pulse therapy with cyclophosphamide in one case (4.3%). Intravenous gammaglobulin was indicated for four patients (17.3%), thalidomide for one (4.3%) and D-penicillamine was given to one patient (4.3%).

Furthermore, 15 of the 23 patients were given specific treatment for calcinosis: diltiazem in six cases (26%), ethylenediaminetetraacetic acid (EDTA) in five (22%) and alendronate in four (17.3%) cases. Corticosteroid (triamcinolone hexacetonide) infiltration of the calcinosis was attempted with one patient. Surgical excision only proved necessary for the patient who developed calcinosis on the urethra.

The clinical, laboratory and treatment characteristics associated with the presence of calcinosis are given in Tables 3 and 4.

The univariate analysis demonstrated that cardiac ( $p = 0.01$ ) and pulmonary ( $p = 0.02$ ) involvement and the need for one or more immunosuppressor (methotrexate, cyclosporine A and/or pulse therapy with intravenous cyclophosphamide) to treat JDM ( $p = 0.02$ ) were associated with increased frequency of calcinosis (Table 3). None of the patients with pulmonary involvement had the anti-Jo-1 antibody.

The multivariate analysis by logistic regression took the presence of calcinosis as dependent variable and the independent variables cardiac involvement, pulmonary involvement and treatment with one or more immunosuppressor. This statistical analysis demonstrated that cardiac involvement ( $p = 0.018$ ; OR = 15.56; 95%CI 1.59-152.2) and the use of one or more of the immunosuppressors listed above ( $p = 0.037$ ; OR 4.01; 95%CI 1.08-14.87) were the only independent variables associated with the presence of calcinosis (Table 4).

Calcinosis had no associations with demographic data. Age over 6.5 years (the mean age at onset) at disease onset was observed in 12 (52%) patients with calcinosis as against 19 (61%) without calcinosis ( $p = 0.25$ ). A period of more than 1 year (the mean duration observed) between onset of the disease and diagnosis elapsed in 11 (48%) cases with calcinosis compared with four (13%) without calcinosis ( $p = 0.31$ ).

Further to this there were no statistical differences between the groups with and without calcinosis in terms of:

**Table 3** - Univariate analysis of demographic, clinical, laboratory and treatment characteristics associated with calcinosis in 54 patients with juvenile dermatomyositis

Characteristics, n (%) or mean $\pm$ SD	Calcinosis (n = 23)	No calcinosis (n = 31)	p
Female sex	16 (70)	25 (81)	0.34
Age at diagnosis in years	6.56 $\pm$ 2.6	7.41 $\pm$ 2.78	0.37
Time between disease onset and start of treatment, in years	1.0 $\pm$ 1.7	0.64 $\pm$ 0.88	0.34
Muscle strength levels I, II or III	12 (52)	15 (48)	1.0
Muscle strength level IV	11 (48)	16 (52)	1.0
$\uparrow$ CK	7 (30)	18 (58)	0.09
$\uparrow$ AST	15 (65)	23 (74)	0.32
$\uparrow$ ALT	13 (57)	19 (61)	1.0
$\uparrow$ LDH	19 (83)	25 (81)	1.0
Pulmonary involvement	10 (43)	5 (16)	0.02
Cardiac involvement	7 (30)	1 (3)	0.01
Gastrointestinal involvement	9 (39)	13 (42)	0.33
Treated with one or more immunosuppressor	15 (65)	10 (32)	0.02
Deaths	2 (8.7)	2 (6.4)	1.0

ALT = aspartate alanine transferase; AST = aspartate aminotransferase; CK = creatine phosphokinase; LDH = dehydrogenase lactate; SD = standard deviation.

**Table 4** - Multivariate analysis model using logistic regression of variables associated with calcinosis in 54 patients with juvenile dermatomyositis

Dependent variable	Independent variable	OR (95%CI)	Nagelkerke's R <sup>2</sup>	p
Calcinosis	Cardiac involvement	15.56 (1.59-152.2)	0.288	0.018
	Treatment with one or more IS	4.01 (1.08-14.87)		0.037

95%CI = 95% confidence interval; IS = immunosuppressors; OR = odds ratio.

female sex (70 vs. 81%;  $p = 0.34$ ), initial muscle weakness (stages I, II or III: 52 vs. 48%,  $p = 1.0$ ; stage IV: 48 vs. 52%,  $p = 1.0$ ), elevated serum levels of muscle enzymes: CK, AST, ALT and LDH (30 vs. 58%;  $p = 0.09$ ; 65 vs. 74%;  $p = 0.32$ ; 57 vs. 61%;  $p = 1.0$  and 83 vs. 81%;  $p = 1.0$ ; respectively) or gastrointestinal involvement (39 vs. 42%;  $p = 0.33$ ) (Table 3).

Four of the 54 patients with JDM (7%) died and underwent autopsies, two in each group ( $p = 1.0$ ). One of the two patients who had had calcinosis died due to sepsis and the other from multiple perforations secondary to gastrointestinal vasculitis. Both of the deaths of patients without calcinosis were due to sepsis.

## Discussion

This study analyzed 54 patients with JDM from a tertiary specialist pediatric rheumatology center. The clinical manifestations and laboratory findings indicative of JDM observed in this sample were similar to what has been described in the medical literature: reduced muscle strength (91.4-100%), elevated muscle enzyme levels (94-100%), pulmonary involvement (14.3-30%) and cardiac involvement (8.5-36%).<sup>8,11</sup> However, in this sample, evidence of gastrointestinal involvement was observed in 40% of the population in contrast with the 17.1 to 26% described in the literature.<sup>8,11</sup>

Calcinosis affects between 10 and 70% of patients with JDM.<sup>8,11,12</sup> Our study identified this disorder in 43% of the patients and it was associated with severe cases of the disease, where there was cardiac involvement and immunosuppressors had been required.

Dystrophic calcifications are calcium deposits that appear in subcutaneous tissue, muscles, fascia and tendons, with a preference for the upper and lower limbs and traumatized areas, as demonstrated by this population.<sup>18</sup> In this study calcinosis cutis circumscripta predominated, in agreement with the literature.<sup>10,20</sup> One relevant feature was the presence of calcinosis all over the body surface, which had occurred in 1/5 of all cases. These diffuse deposits are associated with severe and long-term cases.<sup>10,18</sup>

As was observed here, calcinosis may precede the diagnosis of JDM, but is generally most common between the first and third years of the disease. Nevertheless, there is a report

of calcinosis emerging 12 years after onset of the inflammatory myopathy.<sup>21</sup>

The etiopathogenesis of calcinosis in JDM is unknown, and to date there are few studies in the medical literature on this aspect. Macrophages and proinflammatory cytokines, such as IL-6, IL-1 and TNF- $\alpha$ , have been observed in calcium fluids.<sup>22</sup> In 2000, Pachman et al.<sup>23</sup> studied the genetic polymorphism of TNF- $\alpha$  and detected that the allele TNF- $\alpha$ -308A was associated with dystrophic calcifications, a prolonged disease course and an elevated level of this proinflammatory cytokine. Recently, in 2006, Pachman et al.,<sup>24</sup> studied five cases of calcinosis of JDM. They investigated calcinosis and reported finding bone proteins, osteopontin, osteonectin and bone sialoprotein in protein extracts while the only mineral identified was hydroxyapatite. Nevertheless, the tissue making up the dystrophic calcifications was distinct from bone, with a high mineral content and an irregular mineral distribution.

Just one study has evaluated the risk factors associated with dystrophic calcification, using univariate and multivariate analysis models. Fisler et al.<sup>17</sup> studied 35 cases and found evidence that calcinosis was associated with delayed diagnosis and start of treatment, increased muscle enzyme levels and prolonged disease duration. Pachman et al.<sup>25</sup> also observed an association between calcinosis and delays in starting treatment. In our study, despite the increased time observed between onset of signs and symptoms and institution of therapy, there was no significant difference between patients with and without in terms of this variable. Nevertheless, calcinosis was associated with systemic involvement and the use of aggressive treatment.

Our univariate analysis demonstrated that the presence of cardiac involvement, pulmonary involvement and use of immunosuppressors were all factors associated with calcinosis. However, the logistic regression model revealed that only cardiac involvement and prescription of cytotoxic agents were independent variables with significance for predicting calcinosis.

There are few descriptions of the cardiac involvement of JDM, although it is known that myocarditis, pericarditis and conductive disorders can occur.<sup>8,11,25-28</sup> Furthermore,

descriptions of cardiac involvement associated with calcinosis are even rarer.<sup>29</sup> In this study, the manifestations of cardiac involvement observed were myocarditis and pericarditis, at disease onset, during activity. No cases involved congestive heart failure or conduction disorders. The association between calcinosis and cardiac involvement is probably due to their both being manifestations of a severe form of the disease with persistent inflammation.

Corticoid therapy is the first therapeutic option for treating active JDM, with a favorable response in 80% of patients.<sup>1,8,10-12,17,30</sup> However, immunosuppressors and intravenous gammaglobulin are drugs that can alter the course of the disease and can be indicated during the initial stages of treatment, with the objective of improving control over disease activity and of reducing the chances of calcinosis emerging; which is how they were used with the majority of patients in this sample. Furthermore, it was also demonstrated that the use of cytotoxic drugs was associated with the development of calcinosis, probably because the same patients had severe forms of the disease and needed these medications.<sup>17,25-32</sup>

The treatment of calcinosis is itself controversial, since spontaneous involution of the condition can even occur.<sup>10,29</sup> Reports exist of good efficacy and absent or rare adverse events being obtained with EDTA, diltiazem and bisphosphonates (alendronate or pamidronate), and also with surgical excision and localized infiltration of triamcinolone hexacetonide,<sup>18,26-33</sup> as was used with some of the patients studied here.

Another aspect worthy of interest was the mortality observed in this sample, caused by infection and systemic disease activity. Autopsy results showed that 5.5% of the JDM patients died from sepsis. One patient complained of recurrent abdominal pains and, at autopsy, there was evidence vasculitis of the mucosa, submucosa and serosa with ulceration and perforation of the gastrointestinal tract. In the literature this last symptom is described as occurring in up to 14% of patients with the disease.<sup>34</sup>

One limitation to this study was the retrospective assessment of the medical records from a single tertiary pediatric rheumatology clinic, covering 16 consecutive years. Additionally, the extremely wide confidence intervals may reflect the small sample size, which is itself a function of the rarity of this disease.

Recently, scales to assess disease activity – the Disease Activity Score (DAS),<sup>35</sup> muscle strength – the Childhood Myositis Assessment Scale (CMAS) and the Manual Muscle Testing (MMT) system<sup>36</sup> – and supplementary assessment tests (capillaroscopy and magnetic resonance imaging)<sup>37</sup> have been used by pediatric rheumatologists to assess JDM. Prospective studies should be carried out to assess the association between calcinosis and disease activity as measured by these instruments.

In conclusion, calcinosis was a frequent finding with JDM and emerged during disease progression. The manifestation was associated with the more severe cases, those that also exhibited cardiac involvement and required immunosuppressant treatment.

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