# High frequency of calcinosis in juvenile dermatomyositis: a risk factor study

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## ABSTRACT

**Objective:** To assess the frequency of calcinosis in patients with juvenile dermatomyositis, and the possible risk factors for that manifestation. **Methods:** Medical record review of 34 patients, with an emphasis on the following characteristics: demographic, clinical and laboratory data; type of treatment; adherence to treatment; disease course (monocyclic, chronic and polycyclic); and disease severity. Patients were divided into two groups as follows: those who developed calcinosis (up to the sixth month of follow-up and after six months of follow-up) and those who did not develop calcinosis. Twenty-seven patients underwent two nailfold capillaroscopies (NFC), which were considered altered when the scleroderma pattern was found. **Results:** The mean age of symptom onset of the 34 patients was 6.5 years, the time until diagnosis was 1.2 years, and 70% were females. Half of the patients had a monocyclic disease course, and only 14.7% had severe vasculitis. Almost 90% of the patients undergoing NFC showed a change on the first assessment, 74% showed a change on the second assessment, and the mean interval between both assessments was 1.6 year. Calcinosis was evidenced in 16 (47.1%) patients. No association was observed between the variables analyzed and the development of calcinosis. **Conclusion:** No risk factors for calcinosis were identified in this study, although that complication was found in half of the patients with juvenile dermatomyositis studied.

**Keywords:** dermatomyositis, risk factors, calcinosis.



## INTRODUCTION

Juvenile dermatomyositis (JDM) is a multisystemic disease, part of a heterogeneous group of acquired inflammatory muscle disorders, and corresponds to 85% of all idiopathic inflammatory myopathies in children.[1] It is characterized by vasculitis, which affects primarily the skin and muscles,[2,3] but can also affect other organs, such as the heart, lung, and gastrointestinal tract.[2]

The five diagnostic criteria originally proposed by Bohan and Peter[4,5] in 1975 have remained as the standard criteria for diagnosing JDM, considering the onset age up to 18 years. However, a number of pediatric rheumatologists consider that the diagnosis of JDM in most patients does not require meeting four of the five criteria.[6]

Nailfold capillaroscopy (NFC) is a complementary test that helps diagnosing JDM and assessing disease activity.[7]

Despite the advances in therapy, JDM remains associated with significant morbidity. In several studies, a significant percentage of patients has persistently active disease, develops calcinosis, and undergoes a significant delay in statural growth.[8–12]

Calcinosis is more common in the pediatric population, affecting 10%–70% of the children and adolescents with JDM, as compared with 30% of the adults.[6,12–15] Although most of the calcinosis cases develop in the first three years after diagnosis, it can appear in up to 20 years after disease onset.[16]

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The presence of calcinosis is associated with a delay in diagnosis, longer time of untreated disease, chronic course, disease severity, and inadequate therapy or resistance to treatment.[9]

This study aimed at assessing the frequency of calcinosis in patients with JDM, in addition to assessing possible risk factors for that manifestation.

## MATERIAL AND METHODS

According to the criteria of Bohan and Peter,[4,5] 57 patients were diagnosed with either definitive JDM (presence of typical cutaneous lesions associated with three of the other criteria) or very probable JDM (presence of typical cutaneous lesions associated with two of the other criteria), being followed up at the Pediatric Rheumatology sector from 1992–2010. Of the 57 patients, 23 with incomplete data were excluded. Patients with overlapping syndrome were not included in the study.

A retrospective analysis was performed based on the medical record review of 34 patients, with an emphasis on the following characteristics: demographic, clinical and laboratory data; type of treatment (corticosteroids and other immunosuppressive drugs); adherence to treatment; course of the disease (monocyclic, chronic and polycyclic); severity of disease; and changes observed in NFC. Adherence to therapy was considered good in the presence of at least 80% agreement between the treatment prescribed by the physician and that performed by the patient, according to the definition used by the World Health Organization.[17] The disease course was defined as follows: monocyclic, when the patients underwent disease remission two years after its onset; polycyclic, in the presence of one or more relapses after disease remission; and chronic, when symptoms persisted for over two years.[18] The severity of vasculitis was defined as the presence of persistent vasculitic lesions unresponsive to usual treatment, cutaneous ulcerations, intestinal vasculitis, or need for intravenous immunoglobulin, thalidomide or cyclophosphamide.

Initially, the patients were divided into two groups as follows: those who had calcinosis and those who had no calcinosis during the course of disease until the end of the study. Later, the calcinosis group was assessed separately as follows: patients developing calcinosis within the first six months of follow-up in the outpatient clinic or those who already had calcinosis prior to beginning the follow-up in the outpatient clinic (initial calcinosis); and patients who developed calcinosis after six months of follow-up in the outpatient clinic (progressive calcinosis). Twenty-seven patients underwent NFC at disease onset and during its course, by use of an optical microscope with 10x and 16x magnifications. The following parameters were assessed on NFC: number of capillaries per millimeter; presence and intensity of capillary deletion; and presence of ectatic, bushy, entangled, or giant capillaries. The scleroderma (SD) pattern was defined as the presence of capillary deletion associated with capillary ectasia and/or giant capillaries.[19] The NFC was considered altered when the SD pattern was present.

To assess the association between qualitative variables, the chi-square test or the Fisher exact test was used. The Student *t* test, Mann-Whitney test and Kruskal-Wallis test were used for comparison between the groups.

## RESULTS

Some features of the 34 patients assessed were as follows: mean age at symptom onset, 6.5 ± 3.9 years; mean time until diagnosis, 1.2 ± 2.0 years; mean disease duration, 5.8 ± 3.6 years; and mean outpatient clinic follow-up time, 4.0 ± 2.8 years (Table 1).

Of the 34 patients studied, 24 (70.6%) were females and 22 (64.7%) were Caucasoid. The disease course was as follows: monocyclic, 17 patients (50%); chronic, 11 (32.4%); and polycyclic, six (17.6%). Disease intensity was severe in only five (14.7%) patients, and cutaneous ulcers were present in four (11.7%).

Twenty-seven patients underwent NFC at disease onset and during its course, with a mean interval of 1.6 year between

**Table 1**
Epidemiological and clinical data of patients with juvenile dermatomyositis (n = 34)

| | |
|---|---|
| Mean age at symptom onset (years) | 6.5 ± 3.9 |
| Mean time until diagnosis (years) | 1.2 ± 2.0 |
| Mean disease duration (years) | 5.8 ± 3.6 |
| Mean follow-up time (years) | 4.0 ± 2.8 |
| Monocyclic course, n (%) | 17 (50) |
| Chronic course, n (%) | 11 (32.4) |
| Polycyclic course, n (%) | 6 (17.6) |
| Severe vasculitis, n (%) | 5 (14.7) |
| Altered initial NFC, n (%) | 24 (88.9) |
| Altered final NFC, n (%) | 20 (74.1) |
| Calcinosis, n (%) | 16 (47.1) |
| Initial calcinosis, n (%) | 6 (17.6) |
| Calcinosis on follow-up, n (%) | 10 (29.4) |

**Table 2**
Relationship between the variables studied and the presence or absence of calcinosis in patients with juvenile dermatomyositis (n = 34)

| | Presence of calcinosis (n = 16) | Absence of calcinosis (n = 18) | P |
|---|---|---|---|
| **Female gender, n (%)** | 10 (62.5) | 14 (77.8) | 0.329 |
| **Caucasoid, n (%)** | 11 (68.7) | 11 (61.1) | 0.642 |
| **Mean age of onset in years (SD)** | 6.3 (3.8) | 6.7 (4.1) | 0.911 |
| **Mean time until diagnosis in years (SD)** | 1.9 (2.7) | 0.6 (0.9) | 0.990 |
| **Mean disease duration in years (SD)** | 6.5 (3.5) | 5.3 (3.7) | 0.870 |
| **Mean follow-up time in years (SD)** | 2.8 (2.4) | 5.0 (2.9) | 0.553 |
| **Disease course (mono-M, poly-P, chronic-C)** | 6M, 3P, 7C | 11M, 3P, 4C | 0.336 |
| **Severe vasculitis, n (%)** | 3 (18.8) | 2 (11.1) | 0.530 |
| **Use of immunosuppressive drugs, n (%)** | 15 (93.7) | 13 (72.2) | 0.100 |
| **Adherence to treatment, n (%)** | 9 (56.2) | 13 (72.2) | 0.331 |
| **Mean time for calcinosis to develop in years (SD)** | 2.6 (1.7) | — | |
| **Total** | 16 | 18 | |

both NFC. Of those 27 patients, 24 (88.9%) had an altered initial NFC, with 91.7% of these patients showing active disease at the time of the exam, and 20 (74.1%) had an altered NFC during disease course, with 70% of these patients showing active disease at the time of the exam.

Calcinosis was identified in 16 (47.1%) patients at the initial exam and/or during follow-up, with a mean time of development after the diagnosis of 2.5 ± 1.9 years (six patients had initial calcinosis, and 10 patients had it during disease course). Of those 16 patients, five (31.3%) were 3 years of age or younger, but showed no statistical difference as compared with the older patients (P = 0.317).

The following parameters showed no association with the development of calcinosis: demographic and clinical features; vasculitis intensity; elevation in muscle enzymes; use of immunosuppressive drugs; adherence to treatment; and NFC changes (Table 2). When assessing separately patients with initial calcinosis, patients developing calcinosis during follow-up, and patients without calcinosis, no statistic difference between the variables was identified, except for the monocyclic course, which was statistically more frequent in the group without calcinosis (P = 0.036).

In the 27 patients undergoing NFC, no association was found between the presence of calcinosis and changes in initial NFC or in NFC during disease course (P = 0.681 and P = 0.432, respectively).

Of the 16 patients with calcinosis, seven had a chronic disease course and nine had a monocyclic or polycyclic course. Chronic disease course showed no association with calcinosis frequency and duration and age of calcinosis appearance during disease course (P = 0.336; 0.144 and 0.374, respectively) (Table 3).

**Table 3**
Association of the type of juvenile dermatomyositis course with frequency and duration of calcinosis and age of calcinosis appearance during disease course

| | Monocyclic | Polycyclic | Chronic | P |
|---|---|---|---|---|
| **Frequency of calcinosis, n (%)** | 6 (37.5) | 3 (18.7) | 7 (43.7) | 0.336 |
| **Mean calcinosis duration in years (SD)** | 2.8 (1.8) | 3.1 (1.9) | 2.6 (1.7) | 0.144 |
| **Mean age of calcinosis appearance during disease course in years (SD)** | 9.2 (4.8) | 8.0 (4.6) | 8.9 (4.4) | 0.374 |

## DISCUSSION

This study showed a high frequency of calcinosis in patients with dermatomyositis, although the risk factors for the development of that late complication were not found. The mean time interval between symptom onset and diagnosis was significantly greater in our patients than that reported in most studies,[8,15,20–22] which might have resulted from the delay in referring patients in our study to the specialist, as we have already reported.[23]

Half of our patients had a monocyclic disease course, while in the study by Huber et al.,[8] 37% had a monocyclic course and 63% had either a polycyclic or chronic course. However, those authors have defined the monocyclic course as when the patient had no disease activity and was not on medication for up to 24 months after the diagnosis, which differed from our definition, since we did not consider medication use.[18] Some of those patients might have initiated their diseases prior to their parents' perception, and, thus, had no truly monocyclic courses.

In our case series, cutaneous ulcers were observed in 11.7% of the patients during disease course, similarly to the frequency reported by Sallum et al.,[12] but lower than those reported in other studies.[6,21] The presence of cutaneous ulcers reflects greater disease severity.

Nailfold capillaroscopy is an important tool to help both the diagnosis and the follow-up of patients with JDM. Some studies have reported a change in the NFC of patients with JDM, evidencing the SD pattern in 60% of them.[24] Our patients showed an agreement between disease activity and FNC changes, both initially and during disease course. Other studies have also correlated FNC changes with disease activity.[7]

Almost half of the patients had calcinosis during disease course, a percentage higher than that reported in most studies on JDM.[6,8,11,15,21,22,25–27] One possible explanation for the elevated incidence of calcinosis in our population is the delay in diagnosis, and, thus, a longer duration of disease activity. The disease course in patients without calcinosis was sufficiently long for the appearance of calcinosis, allowing us to characterize those patients as non-candidates to the appearance of that complication. Calcinosis is known to result from persistent disease activity, poor treatment adherence, and therapy refractoriness.[3,9,22,28] It is worth emphasizing that calcinosis manifested in 10 patients during disease course even after six months of beginning therapy and in patients with good adherence to treatment, and no association was observed between non-adherence and the appearance of that complication. The association of age and higher frequency of calcinosis has neither been reported in other studies, nor found in ours.

Despite the high frequency of calcinosis, no risk factors for that complication was evidenced in our study. While some studies[6,8] have found no association between calcinosis and time until diagnosis, others[11,22] have reported a higher frequency of calcinosis in patients with a longer time until diagnosis, and, consequently, a longer time until the beginning of treatment. Another study has reported that early treatment with high doses of corticoid was predictive for not developing calcinosis.[9] Some studies have assessed the relationship between disease course and the presence of calcinosis, but have found no association.[6,8] In our study, 11 of the 17 patients with a monocyclic disease course did not develop calcinosis, suggesting that a better prognosis might be associated with the lower frequency of that complication. In contrast, chronic inflammatory disease might have predisposed to its development. However, in our study, a higher frequency of calcinosis was not observed in any of the disease courses. The use of more than one immunosuppressive agent has been associated with the development of calcinosis in the study by Sallum et al.,[26] showing that calcinosis is associated with most severe disease.

This study is important, because it showed the presence of calcinosis in half of the patients with JDM. Nevertheless, we could not demonstrate the presence of risk factors for the development of that complication. Sample size was a limiting factor. Outcome and occasionally multicenter studies might solve that problem. To our knowledge, no studies assessing the association between calcinosis and NFC changes have been published.

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