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Early Abnormal Nailfold Capillary Changes Are Predictive of Calcinosis Development in Juvenile Dermatomyositis

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ABSTRACT. ***Objective.*** The long-term outcomes of juvenile dermatomyositis (JDM) are more favorable in recent years. However, calcinosis is still among the complications that can cause serious functional impairment. Little is known about the pathogenesis and risk factors of calcinosis. The aim of this study is to determine risk factors for the development of calcinosis in JDM.

Methods. This was a single-center, retrospective cohort study. All patients were diagnosed and followed at the multidisciplinary JDM clinic of The Hospital for Sick Children, from January 1, 1989, until May 31, 2018. To investigate predictors of incident calcinosis, Cox regression analysis was performed.

Results. A total of 172 patients met inclusion criteria, with a median age at diagnosis of 7.7 years (IQR 4.9-12.1), and a median follow-up of 8.5 years (IQR 3.4-12.6, range 0.1-28.3). The only risk factor significantly associated with the development of calcinosis in the univariate analysis was nailfold abnormality at baseline (hazard ratio [HR] 4.86, $P = 0.03$). In multivariable analysis, including nailfold abnormality, age of diagnosis, sex, and duration from onset to diagnosis, the only statistically significant risk factor for calcinosis was the presence of nailfold abnormalities (HR 4.98, $P = 0.03$). Further, calcinosis was significantly increased in patients with a chronic course (chi-square 25.8, $P < 0.001$).

Conclusion. The presence of abnormal nailfold capillary changes at baseline is predictive for the development of calcinosis in children with idiopathic inflammatory myopathies.

Key Indexing Terms: cohort studies, dermatomyositis, risk factors

Juvenile dermatomyositis (JDM) is a rare, chronic, disabling disease that occurs in childhood. It affects about 2 to 3 per million children each year.[1,2] It is a systemic autoimmune disease characterized by chronic muscle weakness and skin manifestations, but it may also affect other organs.[3-5]

The course and severity of this disease is highly variable, but disease course is often divided into 3 types: monocyclic, polycyclic, and chronic.[6] The long-term outcomes of the disease have been favorable in recent years, owing to glucocorticoids and several treatment options such as methotrexate (MTX) and immunoglobulin (Ig); as a result, mortality with JDM has become much lower. In addition, although > 60% of patients will develop organ damage, the most frequently affected organ is skin, and only a small percentage of patients develop serious functional disability.[7,8]

However, calcinosis is still among the complications that can cause serious functional impairment. This condition is based on the presence of dystrophic calcification in subcutaneous, myofascial, or muscle tissues, and this complication is the hallmark sequelae of JDM. Dystrophic calcification occurs at sites of injured tissue with generally normal serum calcium and phosphorous levels.[9] In related conditions, including adult DM and systemic sclerosis, dystrophic calcification is often seen.[10] Calcinosis can be observed and felt on physical examination; however, imaging modalities such as plain radiography and ultrasound can confirm the diagnosis.[11] Despite the recent progress in treatment, calcinosis remains one of the most critical complications and occurs in about 20% to 47% of patients with JDM.[7,12,13] This wide variation in the prevalence of calcinosis in JDM cohorts may depend on the duration of follow-up and the treatment approaches used. Little is known about the pathogenesis and risk factors of calcinosis in JDM.

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The aim of this study was therefore to determine the clinical and basic laboratory risk factors present at baseline that are associated with the development of calcinosis in JDM, using an inception cohort of patients.

METHODS

Study population and data collection. This was a single-center, retrospective, inception cohort study. All patients were diagnosed and followed at the multidisciplinary JDM clinic of The Hospital for Sick Children (SickKids), from January 1, 1989, until May 31, 2018.

Patient inclusion criteria were as follows: (1) age < 18 years at diagnosis; (2) classified as probable or definite according to the American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria for adult and juvenile idiopathic inflammatory myopathies (IIMs)[14]; and (3) inception patients, that is, diagnosed at our clinic or referred to our clinic within 4 months of diagnosis, with satisfactory information regarding clinical and laboratory features at the time of diagnosis (regardless of any treatment). Patients were excluded if any of the above criteria were not met. Calcinosis diagnosis was based on clinical examination findings and/or radiological imaging.

Patients had been treated in a protocol-based manner; we had recommended that all patients be treated, at the outset, with high-dose corticosteroids (prednisone in divided doses orally, unless intravenous (IV) methylprednisolone (MP) pulse was clinically indicated). Since 1997, all patients had been concomitantly treated with MTX (15 mg/m^2) orally or subcutaneously. In corticosteroid-resistant or corticosteroid-dependent cases, we considered the addition of IV Ig and, rarely, cyclophosphamide or other immunosuppressive drugs such as mycophenolate mofetil or calcineurin inhibitors for more seriously ill patients.

At SickKids, all patients with JDM are followed in the JDM clinic until they are 18 years old, and they are then transitioned to St. Michael's Hospital, an adult myositis clinic, regardless of patient status. We collected information for the adult patients who had transitioned to St. Michael's Hospital as part of our inception cohort.

Prognostic factors. We evaluated the following: sex, age at diagnosis, duration from onset to diagnosis, racial ancestry, initial dose of prednisone, IV MP pulse (yes/no), baseline laboratory tests and baseline symptoms such as the presence or absence of skin manifestations (Gottron papules, heliotrope rash, and skin ulcer), mouth ulcer, swallowing disturbance or vocal abnormality, nailfold capillary abnormality, muscle contractures, and abnormal gait. Data regarding nailfold capillary abnormalities, comprising capillary dropout, branching, dilation, tortuosity, areas of hemorrhage, giant capillaries, and decrease in capillary density to < 6 capillary loops/mm, were collected at every ambulatory visit using a stereoscopic microscope or handheld microscope, which are in the clinic for that purpose. For our analysis, changes in nailfold capillaries were grouped and reclassified as abnormal or normal overall, since not all capillary descriptions were consistently recorded at each visit.

In addition, the modified Disease Activity Score (DASm), skin DAS (SDAS), musculoskeletal DAS (MDAS), and the Childhood Health Assessment Questionnaire at baseline were included.[15]

As laboratory data, we reviewed white blood cell count, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio, hemoglobin, platelet count, erythrocyte sedimentation rate, creatine kinase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, creatinine, antinuclear antibody (positive; > 1:160), and myositis-specific autoantibodies (MSAs).

The disease course was classified as follows: monocyclic (if the patient went into remission on therapy, was able to taper treatment after 2 or 3 years, and there was no recurrence following therapy discontinuation), polycyclic (if the patient had flares of the disease with intervals without manifestations and therapy), or chronic (if therapy lasted > 4.5 years and symptoms were drug dependent).[16]

Statistical analysis. Descriptive statistics were used to describe the demographics of the patient population. Continuous variables were expressed as median values with IQR. Categorical variables were presented as percentages. The relationship between calcinosis and disease course was calculated using chi-square analysis. Cox regression analysis was performed to investigate predictors of incident calcinosis. First, each of the possible predictive variables was tested in a univariable Cox regression. Then, multivariable Cox regression analyses including covariates were performed, while controlling for age of diagnosis, sex, and duration from onset to diagnosis, as these individual covariates had been found in other studies to be associated with development of calcinosis.[7,12,13] A P value < 0.05 was considered statistically significant in the multivariable analysis. All statistical analyses were performed using R version 3.4.3 (R Foundation for Statistical Computing).[17, 18]

Statement of ethics and consent. The Research Ethics Boards at SickKids (REB#1000057131) and St. Michael's Hospital (REB#17-171) approved this study. A waiver for consent was granted because the study posed minimal risk, the number of subjects in the review was considered large, and many subjects had been studied years in the past and were not being followed currently.

RESULTS

Study population. There were 230 patients in our JDM database. Of these patients, 58 were excluded (4 were diagnosed before 1989, 17 did not satisfy ACR/EULAR classification criteria or were primarily treated at other centers, 5 had insufficient data, 15 did not have at least 3 visits by the study end date, and 17 were not referred to our clinic within 4 months since starting treatment). A total of 172 patients were included in the final tally, and their demographics are shown in Table 1. One hundred sixty-four patients (95.3%) had definite juvenile IIM and 8 (5%) had probable juvenile IIM; the vast majority had the JDM phenotype. One hundred ten patients (64%) were female. The median age at diagnosis of myositis was 7.7 (IQR 4.9-12.1) years. The median time from the onset of myositis to diagnosis was 3.0 (IQR 1.6-6.2, maximum 48.0) months. The median duration of follow-up was 8.5 (IQR 3.4-12.6, range 0.1-28.3) years.

Characteristics of patients with calcinosis. Table 2 shows the patients' symptoms, laboratory findings, and treatments associated with JDM. Calcinosis was found in 44 patients (25.6%). In 3 patients (1.7%), calcinosis had already presented at the time of diagnosis, and in 41 patients it occurred during the follow-up period (23.8%). Sixteen patients (36%) were male, and 28 patients (64%) were female. The age of diagnosis in patients with calcinosis was 7.1 (IQR 4.7-11.9) years. In these 44 patients, the median time from the onset of JDM to development of calcinosis was 2.1 (IQR 0.95-4.2, maximum 11.6) years. In the patients with calcinosis, the median time from symptom onset to beginning treatment was 2.7 (IQR 1.0-6.2, maximum 48.0) months (data not shown). All the patients had received some treatment for JDM.

Risk factors for calcinosis. The only risk factor significantly associated with the development of calcinosis in the univariate analysis was nailfold abnormality at baseline (hazard ratio [HR] 4.86, P = 0.03). In multivariable analysis, including nailfold abnormality, age of diagnosis, sex, and duration from onset to diagnosis, the only statistically significant risk factor for calcinosis was the presence of nailfold abnormality (HR 4.98, P = 0.03; Table 3).

Table 1. Patient demographics.

	N = 172
Sex (female/male), n	110/62
EULAR/ACR classification for adult and juvenile IIM (definite/probable), n	164/8
Clinical diagnosis, n	
JDM	165
Juvenile polymyositis	5
Overlap syndrome	2
Age at diagnosis, yrs	7.7 (4.9-12.1)
Duration from onset to diagnosis, months	3.0 (1.6-6.2)
Time period of diagnosis, n (%)	
1989-1999	58 (33.7)
2000-2009	63 (36.6)
2010-2017	51 (29.7)
Duration of follow-up, yrs	8.5 (3.4-12.6), range (0.1-28.3)
Disease course	
Monocyclic	54 (31)
Polycyclic	11 (6)
Chronic	68 (40)
Not classified	39 (23)
Total follow-up of the cohort, patient-yrs	1473.7
Baseline DASm (n = 154)	7 (5-9)
Baseline SDAS (n = 154)	2 (2-3)
Baseline MDAS (n = 154)	5 (3-6)
Baseline CMAS (n = 93)	31 (15-43)
Baseline CHAQ (n = 124)	1.1 (0.4-1.8)

Values are expressed as median (IQR) unless indicated otherwise. ACR: American College of Rheumatology; CHAQ: Childhood Health Assessment Questionnaire; CMAS: Childhood Myositis Assessment Scale; DASm: modified Disease Activity Score; EULAR: European Alliance of Associations for Rheumatology; JDM: juvenile dermatomyositis; MDAS: Musculoskeletal Disease Activity Score; SDAS: Skin Disease Activity Score.

Association between calcinosis and disease course of JDM. The disease course was monocyclic, polycyclic, chronic, and not classifiable (had not yet been followed long enough to be classified) in 54 (31%), 11 (6%), 68 (40%) and 39 (23%) of the 172 patients, respectively (Table 1). Further, of the 44 patients who presented with calcinosis, 4 (9%) were monophasic, 3 (7%) were polyphasic, 31 (70%) were chronic, and 6 (14%) were not classifiable. Calcinosis was significantly increased in patients with a chronic course (chi-square 25.8, $P < 0.001$; data not shown).

Association between calcinosis and race. The majority of our patients were of European ancestry (114 [66%]), while the remainder were of Asian (37 [22%]), Afro-Caribbean (9 [5%]), Hispanic (4 [2%]), Native Canadian (1 [1%]), and mixed ancestry (7 [4%]). Of the 44 patients who presented with calcinosis, 24 (55%) were of European, 11 (25%) were of Asian, 3 (7%) of Afro-Caribbean, 3 (7%) of Hispanic, 2 (5%) of mixed, and 1 (2%) of Native Canadian ancestry.

Measurement of myositis-specific antibodies. Twelve patients had MSA testing. The results of MSA testing were as follows: anti-transcriptional intermediary factor 1 (TIF1)-γ (0/8, 0%), antinuclear matrix protein 2 (anti-NXP2; 0/8, 0%), antimelanoma differentiation-associated gene 5 antibody (anti-MDA5; 0/8, 0%), anti-Jo1 (1/11, 9%), anti-PL7 (0/12, 0%), anti-PL12 (0/12, 0%), anti-OJ (0/12, 0%), anti-EJ (0/12, 0%), anti-Mi-2 (0/4, 0%), anti-Mi-2-α (0/8, 0%), anti-Mi-2-β (0/8, 0%), anti-SAE1 (0/8, 0%), and anti-signal recognition particle (SRP; 2/10, 20%; data not shown). None of the patients who presented with calcinosis tested positive for MSAs.

Table 2. JDM-associated symptoms and laboratory findings at baseline.

	n (%)
Gottron papules (n = 172)	135 (78)
Heliotrope rash (n = 172)	114 (66)
Skin ulcer (n = 172)	19 (11)
Nailfold abnormality (n = 169)	141 (83)
Mouth ulcer (n = 172)	30 (17)
Raynaud phenomenon (n = 164)	10 (6)
Dactylitis (n = 172)	10 (6)
Lipodystrophy (n = 172)	1 (0.6)
Calcinosis (n = 172)	3 (2)
Muscle contractures (n = 166)	36 (22)
Arthritis/arthralgia (n = 172)	72 (42)
Abnormal gait (n = 172)	96 (56)
Swallow disturbance or vocal abnormality (n = 172)	44 (26)
Interstitial lung disease (n = 172)	5 (3)
Fever (n = 172)	37 (22)
WBC count, × 10^9/L (n = 171)	7.2 (5.7-8.7)
Neutrophil count (× 10^9/L) (n = 166)	3.9 (2.9-5.2)
Lymphocyte count (× 10^9/L) (n = 166)	2.1 (1.5-2.8)
Neutrophil-to-lymphocyte ratio (n = 166)	1.8 (1.3-2.7)
Hemoglobin, g/L (n = 172)	121 (114-133)
Platelet count, × 10^9/L (n = 172)	293 (242-349)
ESR (n = 170)	19 (7-35)
CK, U/L (n = 171)	327 (99-3248)
AST, U/L (n = 172)	88 (44-219)
ALT, U/L (n = 172)	55 (29-136)
Albumin (n = 162)	41 (37-44)
Creatinine (n = 171)	33 (27-42)
ANA positive, ≥ 160 (n = 156)	78 (50)
Prednisolone dose, mg/kg	1.7 (1.1-2.0)
Use of IV MP within 2 months upon diagnosis	54 (31)

Values are expressed as median (IQR) ALT: alanine aminotransferase; ANA: antinuclear antibody; AST: aspartate aminotransferase; CK: creatine kinase; ESR: erythrocyte sedimentation rate; IV: intravenous; JDM: juvenile dermatomyositis; MP: methylprednisolone; WBC: white blood cell.

DISCUSSION

In our inception cohort of patients with juvenile IIM (the vast majority classified as JDM), of whom approximately 26% developed calcinosis, we found that the only clinical and basic laboratory feature at baseline predictive of the time to develop calcinosis was nailfold capillary abnormalities. Additionally, those with a chronic course were much more likely to develop calcinosis. This suggests that worsening vasculopathy over time leads to more tissue damage, and therefore more scarring (dystrophic calcium deposition).

The prevalence of calcinosis in our patients was similar to previous studies.[7,12,13] Generally, the onset of calcinosis is most often 1 to 3 years after illness onset, but calcinosis has been reported to occur from the time of illness onset to as long as 20

Table 3. Risk factors of calcinosis in JDM (n = 44).

	Univariate Cox Regression			Multivariable Cox Regression		
	HR	95% CI	*P*	HR	95% CI	*P*
Sex (male)	1.20	0.65-2.22	0.56	1.395	0.75-2.61	0.30
Age of diagnosis	1.00	0.94-1.08	0.91	1.01	0.93-1.08	0.83
Months from onset to diagnosis	1.01	0.98-1.05	0.46	1.01	0.98-1.05	0.46
Use of intravenous methylprednisolone at diagnosis within 2 months	1.21	0.66-2.24	0.54	-	-	-
Initial prednisolone dose (mg/kg)	1.35	0.83-2.20	0.23	-	-	-
Swallow disturbance or vocal abnormality	1.59	0.85-2.97	0.14	-	-	-
Mouth ulcer	0.74	0.31-1.76	0.50	-	-	-
Raynaud phenomenon	0.29	0.04-2.13	0.23	-	-	-
Dactylitis	0.36	0.05-2.63	0.32	-	-	-
Fever	1.14	0.56-2.30	0.73	-	-	-
Gottron papules	1.60	0.71-3.60	0.25	-	-	-
Heliotrope rash	1.80	0.89-3.65	0.10	-	-	-
Skin ulcer	1.92	0.89-4.15	0.10	-	-	-
Nailfold abnormality	4.86	1.18-20.07	0.03	4.98	1.20-20.68	0.03
Muscle contractures	1.25	0.63-2.48	0.53	-	-	-
Abnormal gait	1.75	0.93-3.31	0.08	-	-	-
Arthritis/arthralgia	1.54	0.85-2.78	0.15	-	-	-
Baseline CHAQ	0.85	0.51-1.39	0.51	-	-	-
Baseline DASm	1.12	0.98-1.28	0.11	-	-	-
Baseline MDAS	1.08	0.94-1.25	0.28	-	-	-
Baseline SDAS	1.25	0.92-1.70	0.15	-	-	-
Baseline height *z* score	0.93	0.71-1.21	0.57	-	-	-
Baseline weight *z* score	0.88	0.67-1.14	0.33	-	-	-
Baseline BMI	1.00	0.93-1.08	0.98	-	-	-
WBC	0.99	0.88-1.11	0.83	-	-	-
Neutrophil	1.00	0.87-1.16	0.98	-	-	-
Lymphocyte	0.86	0.64-1.16	0.31	-	-	-
Neutrophil-to-lymphocyte ratio	1.02	0.94-1.11	0.61	-	-	-
Log (neutrophil-to-lymphocyte ratio)	1.61	0.63-4.08	0.32	-	-	-
Hemoglobin	0.99	0.97-1.01	0.46	-	-	-
Platelet	0.998	0.995-1.00	0.27	-	-	-
ESR	1.00	0.99-1.02	0.57	-	-	-
logCK	1.00	0.71-1.43	0.98	-	-	-
AST	1.00	1.00-1.003	0.09	-	-	-
ALT	1.00	0.998-1.00	0.74	-	-	-
Albumin	0.96	0.91-1.02	0.19	-	-	-
Creatinine	0.98	0.96-1.01	0.20	-	-	-
ANA positive	0.73	0.40-1.34	0.31	-	-	-

ALT: alanine aminotransferase; ANA: antinuclear antibody; AST: aspartate aminotransferase; CHAQ: Childhood Health Assessment Questionnaire; CK: creatine kinase; DASm: modified Disease Activity Score; ESR: erythrocyte sedimentation rate; JDM: juvenile dermatomyositis; MDAS: Musculoskeletal Disease Activity Score; SDAS: Skin Disease Activity Score; WBC: white blood cell.

years later.[19-21] In our study, the median number of years from the onset of JDM to calcinosis was 2.1, and compared to previous studies, there was no major difference.

So far, risk factors for calcinosis in patients with JDM are not well understood and information has been largely limited to a few studies. The previous studies that have reported risk factors regarding calcinosis in JDM have suggested that calcinosis is associated with a longer duration of untreated disease, younger age at disease onset, and more severe disease.[7,12,22-24] In our study, calcinosis was significantly increased in patients with a chronic course. We speculate that more aggressive treatment, to reduce disease activity earlier, may prevent calcification; further studies would be beneficial. Also, geographic location and racial differences have been shown to be associated with the risk of calcinosis.[7] For example, a higher rate of calcinosis was observed in South America than in Europe, and African American and male patients were observed to have a higher risk of calcinosis. The majority of our subjects were of European ancestry, and the remainder were mostly of Asian descent. Likewise, we could not determine the relationship between ancestry and calcinosis in those from European vs Asian descent. In addition, several studies have reported an association between calcinosis and anti-NXP-2 antibody.[23,25,26] More recently, in a Turkish cohort, calcinosis was observed in 75% of patients who were anti-MDA5 positive, and in 50% of those who were NXP-2 and TIF1-γ positive. Calcinosis was even detected at the onset of JDM in 50%

of patients who were MDA5 positive and 10% of those who were NXP-2 positive.[27] This finding suggests that anti-MDA5 antibody positivity is, perhaps, a more important predictive factor for the development of calcinosis than anti-NXP-2 antibody positivity. However, since the sample size in the Turkish cohort was very small, this conclusion requires further study. At the time our patients were studied, we did not have MSA testing locally available; only those patients who had unusual disease features had blood sent out of province for reference laboratory MSA tests. Therefore, only 12 of our patients were tested for MSAs; none of the patients who presented with calcinosis tested positive for MSAs.

Although we could not reliably include race/ethnicity or MSA as prognostic factors, we evaluated many factors that might predict calcinosis. As our results show, the only baseline risk factor for calcinosis that we found was abnormal nailfold capillaries.

Abnormal nailfold capillaries are one of the particular manifestations in JDM.[28] Nailfold capillaroscopy is a noninvasive, reproducible technique that provides information about abnormalities in periungual microvasculature.[29] In this method, the small vessels around the nailfolds are visualized, and detected changes are thought to mirror microvascular abnormalities in other organs. Capillaroscopy has been widely used to evaluate the diagnosis, course, and progression of childhood and adult dermatomyositis and systemic sclerosis.[30-33] Mainly, the findings include capillary dropout, capillary dilatation, and bushy loops.[28,34] Capillaroscopy examination often takes into account quantitative measurements of capillary density or end-row loop loss, in addition to the presence of avascularity and abnormal capillaries represented as "bushy" or "bizarre" loops.[35] The degree of morphologic nailfold changes appears to correlate with the clinical course of JDM. So far, several studies, including our inception cohort, have reported the association between nailfold capillaroscopy density and disease activity.[36-38] Nailfold capillaroscopy showed abnormal capillaries in 83% of our patients. According to previous studies, nailfold capillaroscopy changes have been reported to range from 35% to 68%, which might depend on patient selection for evaluation.[27,39-41] In an American cohort, the odds of having calcinosis were reported to be approximately 9 times higher for patients who had ever had periungual capillary changes compared to patients who had not.[42] Previous research has not examined the relationship between calcinosis and abnormal nailfold capillary changes at baseline, and therefore our study, using longitudinal analysis, presents new and important information.

A major limitation of our study is that we could not evaluate the effect of MSAs for calcinosis due to including older patients diagnosed more than a quarter century ago. The numbers of tested patients over the years have been low because (1) our early study showed a low frequency of identified antibodies, and (2) it is only in the last few years that we have had routine testing available to us.[43] If, indeed, calcinosis is associated with specific MSA such as anti-NXP-2 and anti-MDA5, this may have added important predictive power. Also, we did not record quantitative measurements of capillary density and the actual pattern consistently enough for those to be analyzed; rather, we assessed the nailfold capillaries as normal or abnormal. By measuring capillary density, we might be able to demonstrate a relationship between the extent of vasculopathy and risk of calcinosis in JDM.

In conclusion, we suggest that the presence of abnormal nailfold capillary changes, at baseline, and following a chronic disease course, are predictors for the development of calcinosis in children with IIM.

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