Full-length Manuscript

Short running head: Predictors of JDM calcinosis

Full title of manuscript:

Early abnormal nailfold capillary changes are predictive of calcinosis development in juvenile dermatomyositis.

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The source(s) of support in the form of grants or industrial support: Tomo Nozawa was supported by research fellowships of Japan Society of Allergology, Mochida Memorial Foundation, and Gushinkai. Brian Feldman is supported by the Ho Family Chair in Autoimmune Diseases.

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Conflict of Interests: The authors have no potential conflicts of interest relevant to this article to disclose.

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Key Index Terms: cohort studies, dermatomyositis, risk factors

Statement of ethics and consent:

The Research Ethics Boards at SickKids (REB#1000057131) and St. Michael's Hospital (REB#17-171) approved this study.

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 Hospital for Sick Children's multidisciplinary JDM clinic, 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, median age at diagnosis of 7.7 years (interquartile range [IQR] 4.9-12.1), median follow-up of 8.5 years (IQR 8.5-12.6, range 0.13-28.3). The only risk factor significantly associated with the development of calcinosis in the univariate analysis was nailfold abnormality at baseline (hazard ratio [HR] 4.857, p = 0.029), and the other variables had no significant relationship with calcinosis. 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 4.975, p = 0.027). Furthermore, calcinosis was significantly increased in patients with a chronic course (chi-square 25.8, p = 0.00001).

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

INTRODUCTION

Juvenile dermatomyositis (JDM) is a rare, chronic, disabling disease of childhood. It affects about 2-3 per million children each year (1, 2). It is a systemic autoimmune disease characterized by chronic muscle

weakness and skin manifestations, but may also affect other organs (3-5).

The course and severity of this disease is highly variable, but disease course is often divided into three types: monocyclic, polycyclic, and chronic (6). The long-term outcomes of the disease are favorable, in recent years, owing to glucocorticoids and several treatment options such as methotrexate and immunoglobulin; mortality with JDM has become much lower. In addition, although greater than 60% of patients will develop organ damage, the most frequently affected organ is skin and only a small percentage of patients have 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 dermatomyositis 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, it remains one of the most critical complications and occurs in about 20-47% of patients with JDM (7, 12, 13). This wide variation of the prevalence of calcinosis in JDM cohorts may depend on the duration of follow-up and the treatment approaches utilized. Little is known about the pathogenesis and risk factors of calcinosis in JDM. The aim of this study was therefore to determine the clinical and basic laboratory risk factors, present at baseline, for the development of calcinosis in JDM using an inception cohort of patients.

PATIENTS AND METHODS

Study population and data collection.

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

Patient inclusion criteria were as follows: 1) age <18 at diagnosis; 2) classified as probable or definite

according to ACR/EULAR Rheumatology Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies (14); 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 have 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 IV pulse methylprednisolone is clinically indicated). Since 1997, all patients have been concomitantly treated with methotrexate (15 mg/m2) orally or subcutaneously. In corticosteroid-resistant or corticosteroid dependent cases, we consider the addition of intravenous immunoglobulin 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 up 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 patients' status. We collected information for the adult patients who had transitioned to St. Michael's Hospital as part of our inception cohort. 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 no more than minimal risk, the number of subjects in the review was considered large, and because many subjects had been studied years in the past and were not being followed currently.

Prognostic factors.

We evaluated the following: sex, age at diagnosis, duration from onset to diagnosis, racial ancestry, initial dose of prednisone, intravenous methylprednisolone 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 overall abnormal or normal, 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 (CHAQ) 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, creatinine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, creatinine, antinuclear antibody (positive; >1:160), and myositis-specific autoantibodies (MSAs).

The disease course was classified as 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 patients had flares of the disease with intervals without manifestations and without therapy) and chronic (if the therapy lasted more than 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 interquartile range. Categorical variables were presented as percentages. The relationship between calcinosis and disease course was calculated using a 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 then 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. A P value of less than 0.05 was considered statistically significant in the multivariable analysis. All analyses were performed using R version 3.4.3 (17, 18).

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 EULAR/ACR classification criteria or were primarily treated at other centres, 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. The 172 patients' demographics are shown in Table 1. One hundred sixty-four (95%) patients had definite juvenile idiopathic inflammatory myopathies and 8 (5%) had probable; the vast majority had the JDM phenotype. One hundred and ten patients (64%) were females. The median age at diagnosis of myositis was 7.7 years (25th to 75th percentiles: 4.9-12.1 years). The median time from the onset of myositis to diagnosis was 3.0 months (25th to 75th percentiles: 1.63-6.20, maximum 48.00 months). The median duration of follow-up was 8.5 years (25th to 75th percentiles: 8.5-12.6, range 0.13-28.3 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 years (25th to 75th percentiles: 4.72-11.87 years). In these 44 patients, the median time from the onset of JDM to development of calcinosis was 2.1 years (25th to 75th percentiles: 0.95-4.23, maximum 11.63 years). In the patients with calcinosis, the median time from symptom onset to beginning treatment was 2.7 months (25th to 75th percentiles: 1.02-6.24, maximum 48.00 months). 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] 4.857, p = 0.029); the other variables had no significant relationship with calcinosis. 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 4.975, p = 0.027) (Table 3).

Association between calcinosis and disease course of JDM

The disease course was monocyclic, polycyclic, chronic and not classifiable (had not yet been followed up long enough to be classified) in 54 (31%), 11 (6%), 68 (40%) and 39 (23%) of the 172 patients. Furthermore, of the 44 patients who presented with calcinosis, 4 (9%) were monophasic, 3 (7%) were polyphasic, and 31 (70%) were chronic, 6 (14%) were not classifiable respectively. Calcinosis was significantly increased in patients with a chronic course (chi-square 25.8, p = 0.00001).

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 respectively.

Measurement of Myositis Specific Antibodies

Twelve patients had MSA testing. The results of MSA testing were as follows: anti-TIF-1g (0/8, 0%), anti-NXP2 (0/8, 0%), anti-MDA5 (0/8, 0%), anti-Jo-1 (1/11, 9%), anti-PL-7 (0/12, 0%), anti-PL-12 (0/12, 0%), anti-OJ (0/12, 0%), anti-EJ (0/12, 0%), anti-Mi-2 (0/4, 0%), anti-Mi-2-alpha (0/8, 0%), anti-Mi-2-beta (0/8, 0%), anti-SAE1 (0/8, 0%), and anti-SRP (2/10, 20%). None of the patients who presented with calcinosis tested positive for MSAs.

DISCUSSION

In our inception cohort of patients with juvenile idiopathic inflammatory myopathies (the vast majority classified as JDM), of whom ~ 26% developed calcinosis, we found that the only clinical / 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, to us, that worse 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 1-3 years after illness onset, but calcinosis has been reported to occur from the time of illness onset to as long as 20 years later (19-21). In our study, the median years from the onset of JDM to calcinosis is 2.1 years and compared to the 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 which 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; this will be an interesting avenue of study. Also, geographic location and racial differences have been 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 have a higher risk of calcinosis. The majority of our subjects were of European ancestry, and the remainder were mostly of Asian descent. Since there were very few of Afro-Caribbean and Hispanic descent in our study, we could not determine a relationship between ancestry and calcinosis. 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 anti-MDA5 positive patients, and 50% of NXP-2 and TIF1g positive patients. Calcinosis was even detected at the onset of JDM in 50% of MDA5 and 10% of

NXP-2 positive patients (27). This finding has suggested 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 which might predict calcinosis; the only baseline risk factor for calcinosis that we found is abnormal nailfold capillaries.

Abnormal nailfold capillaries are one of the particular manifestations in JDM (28). Nailfold capillaroscopy is a non-invasive, reproducible technique that provides information about abnormalities in periungual microvasculature (29). By this method, the small vessels around the nailfolds are visualized, and detected changes are thought to mirror microvascular abnormalities in other organ; 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, including our inception cohort, several studies 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 without them (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 impact of myositis-specific autoantibodies 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 i) our early study showed a low frequency of identified antibodies, and ii) it's only in the last few years that we have routine testing available to us (43). If, indeed, calcinosis is associated with specific MSA, such as anti-NXP-2 and anti-MDA5 antibody, this may have added important additional 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 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 idiopathic inflammatory myopathies.

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Table 1. Patients' demographics

Characteristics	N=172
Sex (Female/Male)	110/62
EULAR/ACR classification for adult and juvenile IIM, Definite/Probable	164/8
Clinical diagnosis	
Juvenile dermatomyositis	165
Juvenile polymyositis	5
Overlap syndrome	2
Median age (years) at diagnosis (25th, 75th percentile)	7.7 (4.9, 12.1)
Median duration from onset to diagnosis (months) (25th, 75th percentile)	3.0 (1.6, 6.2)
Time period of diagnosis, N (%)	
1989-1999	58 (34)
2000-2009	63 (37)
2010-2017	51 (30)
Median duration of follow-up, years (25th, 75th percentile)	8.5 (3.4, 12.6) range (0.13-28.3)
Disease course	
Monocyclic	54 (31)
Polycyclic	11 (6)
Chronic	68 (40)
Not classified	39 (23)
Total follow-up of the cohort, patient years	1473.69
Median baseline DASm (25th, 75th percentile) (N=154)	7 (5, 9)
Median baseline SDAS (25th, 75th percentile) (N=154)	2 (2, 3)
Median baseline MDAS (25th, 75th percentile) (N=154)	5 (3, 6)

Median baseline CMAS (25th, 75th percentile) (N=93)	31 (15, 43)
Median baseline CHAQ (25th, 75th percentile) (N=124)	1.13 (0.38, 1.75)

EULAR: European Alliance of Associations for Rheumatology; ACR: American College of Rheumatology; DASm: modified disease activity score; SDAS: skin disease activity score; MDAS: musculoskeletal disease activity score; CMAS: Childhood Myositis Assessment Scale; CHAQ: Childhood Health Assessment Questionnaire.

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's 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 ($\times 10^9$/L) (N=171)	7.20 (5.70, 8.65)
Neutrophil count ($\times 10^9$/L) (N=166)	3.89 (2.86, 5.24)
Lymphocyte count ($\times 10^9$/L) (N=166)	2.09 (1.53, 2.82)
Neutrophil/Lymphocyte ratio (N=166)	1.76 (1.25, 2.74)
Hemoglobin (g/L) (N=172)	121 (114, 133)
Platelet count ($\times 10^9$/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)	1.66 (1.06, 2.03)
Use of intravenous methylprednisolone at diagnosis within 2 months	54 (31)

JDM: Juvenile dermatomyositis; WBC: white blood cell; ESR: erythrocyte sedimentation rate; CK: creatinine kinase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ANA: antinuclear antibody.

Table 3. Risk factors of calcinosis in JDM

Calcinosis (N=44)	Univariate Cox regression			Multivariable Cox regression		
	HR	95% CI	P value	HR	95% CI	P value
Sex (Male)	1.199	0.648-2.219	0.563	1.395	0.746-2.610	0.297
Age of diagnosis	1.004	0.936-1.078	0.908	1.008	0.934-1.081	0.834
Months from onset to diagnosis	1.013	0.979-1.048	0.458	1.013	0.979-1.047	0.465
Use of intravenous methylprednisolone at diagnosis within 2 months	1.213	0.656-2.242	0.539			
Initial prednisolone dose (mg/kg)	1.347	0.826-2.197	0.233			
Swallow disturbance or vocal abnormality	1.594	0.854-2.974	0.143			
Mouth Ulcer	0.742	0.314-1.756	0.498			
Raynaud's phenomenon	0.293	0.040-2.130	0.225			
Dactylitis	0.362	0.050-2.629	0.315			
Fever	1.135	0.560-2.298	0.726			
Gottron papules	1.603	0.714-3.596	0.253			
Heliotrope rash	1.804	0.891-3.654	0.101			
Skin Ulcer	1.924	0.893-4.146	0.095			
Nailfold abnormality	4.857	1.175-20.07	0.029	4.975	1.197-20.68	0.027
Muscle contractures	1.247	0.626-2.482	0.530			
Abnormal gait	1.752	0.929-3.305	0.083			
Arthritis/arthralgia	1.538	0.851-2.780	0.154			
Baseline CHAQ	0.845	0.514-1.389	0.507			

Baseline DASm	1.118	0.976-1.280	0.108			
Baseline MDAS	1.083	0.937-1.252	0.281			
Baseline SDAS	1.250	0.919-1.700	0.154			
Baseline Height Z-score	0.926	0.710-1.208	0.571			
Baseline Weight Z-score	0.875	0.671-1.142	0.327			
Baseline Body mass index	1.001	0.929-1.078	0.982			
WBC	0.987	0.875-1.113	0.826			
Neutrophil	1.001	0.868-1.155	0.984			
Lymphocyte	0.858	0.638-1.155	0.314			
Neutrophil/Lymphocyte ratio	1.022	0.939-1.113	0.611			
Log (Neutrophil/Lymphocyte ratio)	1.608	0.634-4.075	0.317			
Hemoglobin	0.992	0.970-1.014	0.456			
Platelet	0.998	0.995-1.001	0.273			
ESR	1.003	0.992-1.015	0.567			
logCK	1.004	0.707-1.426	0.981			
AST	1.001	1.000-1.003	0.091			
ALT	1.000	0.998-1.003	0.736			
Albumin	0.962	0.909-1.019	0.187			
Creatinine	0.984	0.961-1.008	0.196			
ANA positive	0.728	0.395-1.343	0.310			

JDM: Juvenile dermatomyositis; CHAQ: Childhood Health Assessment Questionnaire; DASm: modified disease activity score; MDAS: musculoskeletal disease activity score; SDAS: skin disease activity score; WBC: white blood cell; ESR: erythrocyte sedimentation rate; CK: creatinine kinase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ANA: antinuclear antibody.