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ORIGINAL ARTICLE PEDIATRICS

Initial manifestations and risk factors for calcinosis in juvenile dermatomyositis: A retrospective multicenter study

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ABSTRACT

OBJECTIVE: This study aimed to look for the initial manifestations of juvenile dermatomyositis (JDM), give follow-up results, and search for risk factors for the development of calcinosis.

METHODS: The files of children with JDM diagnosed between 2005 and 2020 were reviewed retrospectively.

RESULTS: The study included 48 children, 33 girls and 15 boys. The mean age at the onset of the disease was 7.6±3.6 years. The median duration of follow-up was 35 (6–144) months. Twenty-nine patients (60.4%) had monocyclic, 7 (14.6%) patients had polycyclic, and 12 (25%) patients had chronic persistent disease course. At the time of enrollment, 35 (72.9%) patients were in remission, while 13 (27.1%) patients had active disease. Calcinosis developed in 11 patients (22.9%). Children having myalgia, livedo racemosa, skin hypopigmentation, lower alanine aminotransferase (ALT) levels, and higher physician visual analog scores at the time of diagnosis had a higher risk for calcinosis. Calcinosis was also more common in children with diagnostic delay and chronic persistent disease course. None of these parameters remained independent risk factors for calcinosis in multivariate logistic regression analysis.

CONCLUSION: The rate of mortality has decreased dramatically over decades in JDM, but the rate of calcinosis has not changed proportionately. Long duration of active, untreated disease is accepted as the main risk factor for calcinosis. We have seen that calcinosis was more common in children having myalgia, livedo racemosa, skin hypopigmentation, lower ALT levels, and higher physician visual analog scores at the time of diagnosis.

Keywords: Calcinosis; clinical manifestations; juvenile dermatomyositis.

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Juvenile dermatomyositis (JDM) is an autoimmune disease of unknown etiology, primarily affecting muscles and skin. The main characteristics of the disease are inflammation of skeletal muscles and typical skin rashes [1]. JDM may affect any system or organ in the body, including the lungs, gastrointestinal tract, heart, and nervous system [1, 2].

Even though it is the most common form of juvenile idiopathic inflammatory myopathies, the disease is rare in childhood. It is more commonly seen in girls with a female/male ratio of 2–3/1, and the median age at diagnosis is around 7 years [3, 4]. The diagnosis is straightforward for an experienced physician in children presenting with typical skin rashes (i.e., heliotrope rash and Gottron's papules), elevated muscle enzymes, and proximal muscle weakness. Bohan and Peter's criteria, developed in 1975, are still used in clinical trials and research studies [5].

The rate of morbidity and mortality has decreased dramatically with the advent of immunosuppressive treatments in recent decades, but calcinosis seems to remain a challenge for both clinicians and patients [6, 7]. The disease may follow a monocyclic, polycyclic, or chronic persistent course. Description of myositis-specific antibodies (MSAs), each associated with a distinct phenotype and disease course, may help clinicians inform the patients and parents about possible expected outcomes [2, 8, 9].

The study's primary objective was to document the initial clinical and laboratory manifestations of JDM patients and give follow-up results. The secondary objective was to search for risk factors for calcinosis.

Highlight key points

- Juvenile dermatomyositis has the same female predominance, age onset, and skin and muscle manifestations irrespective of the country of origin.
- Mortality has decreased dramatically with contemporary treatment modalities, but the rate of calcinosis has not changed proportionately.
- Long duration of active disease seems to be the main determinant for the development of calcinosis.

MATERIALS AND METHODS

The study was conducted in six pediatric rheumatology centers that are members of the Pediatric Rheumatology Academy-Research Group in Turkiye [10]. The files of children with JDM diagnosed between 2005 and 2020 were reviewed retrospectively. To be included in the study, the child had to fulfill Bohan and Peter JDM criteria (either definite or probable), had to be coming regularly to follow-up visits, and had to have completed the initial 6 months of follow-up. Initial clinical manifestations, laboratory results, medications used, and clinical outcomes were recorded on the case registry forms by the treating physicians.

The disease course was defined as monocyclic (patient achieved remission within 2 years of diagnosis), polycyclic (patient had a recurrence of active disease after a definite time of remission), and chronic persistent (patient did not achieve remission after 2 years of treatment) [2, 11–14]. Remission at the time of enrollment was defined by the PRINTO criteria [15]. The study was approved by the local ethics committee and was performed according to the tenets of the Declaration of Helsinki (date: 29.04.2021, number: B.10.1.TKH.4.34.H.GP.0.01/124). Informed consent was taken from the legal guardians of the children.

Statistical Analysis

The SPSS version 21.0 (SPSS, Inc., Chicago, IL, USA) is used for statistical analysis. The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov–Smirnov/Shapiro–Wilk's test) to determine whether or not they are normally distributed. Quantitative data with normal distribution were presented as mean±standard deviation, and data with nonnormal distribution were presented as median and minimum-maximum. Categorical data were presented as counts and percentages. Categorical variables were compared with the Chi-square test or Fisher's exact test where appropriate. The Mann–Whitney U test was used to compare the non-normally distributed continuous data between two groups. The variables that showed a p-value of 0.05 in the univariate analysis were tested in a multivariate regression analysis. The multivariate linear logistic regression model was used to identify the independent predictor factors for the development of calcinosis. A $p<0.05$ was considered to show a statistically significant result.

RESULTS

The initial cohort included 58 JDM patients. Ten patients were excluded from the study; 3 patients had dropped the follow-up, 4 patients had incomplete initial clinical and laboratory information records, 2 patients had amyopathic dermatomyositis, and 1 patient had mixed connective tissue disease. Finally, 48 JDM patients were included in the study.

Table 1. Demographic features and disease course of the patients (n=48)

Demographics	(%)
Gender	
Female	68.8
Male	31.2
Age at onset (years), mean±SD	7.6±3.6
Age at diagnosis (years), mean±SD	8.2±3.7
Diagnostic delay (months), median (minimum–maximum)	3.0 (1–48)
Follow-up duration (months), median (minimum–maximum)	35.0 (6–144)
Disease course	
Monocyclic	60.4*
Polycyclic	14.6
Chronic persistent	25.0

*: Eleven patients with monocyclic course had follow-up duration of <24 months and they were provisionally classified as having a monocyclic course. SD: Standard deviation.

Table 2. Initial clinical manifestations of the patients

Clinical manifestations	n=48 (%)
Gottron's papules	97.9
Heliotrope rash	95.8
Proximal muscle weakness	89.6
Periorbital edema	79.2
Gower's sign	72.9
Myalgia	62.5
Malar rash	60.4
Subcutaneous edema	50.0
Periungual erythema	45.8
Arthralgia	41.7
Photosensitive rash	35.4
Eyeliner sign	22.9
Linear extensor erythema	16.7
Shawl/V sign	14.6
Raynaud phenomenon	14.6
Skin hyperpigmentation	14.6
Fever	12.5
Skin hypopigmentation	12.5
Livedo reticularis	12.5
Arthritis	10.4
Livedo racemosa	4.2
Skin necrosis	4.2

The cohort comprised 33 girls (68.8%) and 15 boys (31.3%). The mean age at the onset of the first symptom related to JDM was 7.6±3.6 years and the mean age at the diagnosis was 8.2±3.7 years (Table 1). The majority (62.5%) of the cases were diagnosed in the first 3 months of the disease and the median delay between the first symptom compatible with JDM and diagnosis was 3 (1–48) months. Six patients were diagnosed over a year after the initial symptom. The median duration of follow-up was 35 (6–144) months. The disease course was defined as monocyclic in 29 (60.4%) patients, polycyclic in 7 (14.6%) patients, and chronic persistent in 12 (25%) patients (Table 1). Eleven patients with monocyclic courses had follow-up duration of <24 months, and they were provisionally classified as having a monocyclic course.

Initial clinical manifestations and laboratory results of the patients are given in Table 2. All but one patient had Gottron's papules and 46 (95.8%) patients had heliotrope rash. Furthermore, 10 (20.8%) patients had Gottron's papules located other than fingers, mainly on the knees and elbows. Periorbital edema and malar rash were observed in 38 (79.2%) and 29 (60.4%) patients, respectively. Proximal muscle weakness was evident at the time of diagnosis in 43 (89.6%) patients and Gower's sign in 35 (72.9%) patients. Gastrointestinal system involvement, in the form of dysphagia/swallowing dysfunction (5 patients), gastroesophageal reflux (2 patients), and abdominal pain (1 patient), was seen in 8 (17.7%) patients. Six patients had nasonated speech, one patient had interstitial lung disease, and one patient had cardiac involvement reflected as myocarditis.

Magnetic resonance imaging (MRI) of the thighs and pelvic girdle was performed in 36 (75%) patients. MRI revealed myositis in 34 (94.4%) patients and subcutaneous edema and fasciitis without overt myositis in 2 (5.6%) patients. Electromyography (EMG) was done in 40 (83.3%) patients and demonstrated typical JDM myopathy in 33 (82.5%) cases. Muscle biopsy was performed in 17 (35.4%) patients and all were compatible with JDM.

The median values of muscle enzymes and disease assessment scores are shown in Table 3. It was seen that median values of creatinine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) were all elevated;

Table 3. Laboratory results and Visual Analog Scale scores of the patients

Parameter	At the time of diagnosis Median (minimum–maximum)	At the last visit Median (minimum–maximum)
CK, U/L (normal: <200)	1539 (43–16.054)	114 (85–187)
AST, U/L (normal: <40)	123 (19–550)	29 (14–29)
ALT, U/L (normal: <41)	65 (10–689)	11 (7–15)
LDH, U/L (normal: <280)	642 (212–2369)	200 (164–293)
Aldolase, U/L (normal: <7.6)	10.6 (3.8–48)	5.1 (2–7)
Physician VAS	7 (3–10)	0 (0–7)
Patient/parent VAS	7.5 (3–10)	0 (0–8)

CK: Creatinine kinase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; VAS: Visual Analogue Scale.

Table 4. Medications used throughout the disease course

Monocyclic (n=29)	%	Polycyclic (n=7)	%	Chronic persistent (n=12)	%
Corticosteroids (oral)	96.5	Corticosteroids (oral)	100	Corticosteroids (oral)	100
Corticosteroids (pulse)	68.9	Corticosteroids (pulse)	100	Corticosteroids (pulse)	91.6
Methotrexate	93.1	Methotrexate	100	Methotrexate	100
HCQ	20.6	HCQ	42.8	HCQ	33.3
IVIG	13.7	IVIG	71.4	IVIG	83.3
MMF	3.4	MMF	14.2	MMF	66.6
		Cyclosporine	28.5	Cyclosporine	16.6
				Cyclophosphamide	25
				Rituximab	25
				Pamidronate	25
				Infliximab	16.6
				Tofacitinib	16.6
				Etanercept	8.3

HCQ: Hydroxychloroquine; IVIG: Intravenous immunoglobulin; MMF: Mycophenolate mofetil.

1539 U/L, 123 U/L, 65 U/L, and 642 U/L, respectively. LDH was the most commonly elevated enzyme and was normal only in 4 (8.3%) patients. Four of the enzymes were elevated in 27 (56.2%) patients and in 3 (6.2%) patients, only one enzyme (LDH) was elevated. Aldolase levels were measured at the time of diagnosis in 11 patients and were elevated in 9 patients. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels were mildly elevated in 12.5% and 31.2% of the cohort, respectively. The median value of CRP was 1.3 mg/L (0.1–14.4) and ESR was 15 mm/h (5–40). Antinuclear antibody was positive in 43.8% of the patients. MSAs were not available in all centers, and only anti-Jo-1 was searched in 26 patients and became positive in 3 patients. Other MSAs were studied in 6 patients and 3 were positive for anti-MJ, and 1 for anti-p155/p140. Myositis-associated antibodies (MAAs) were studied in 35 patients and two patients had anti-Ro and one patient had anti-La positivity.

Medications used throughout the disease course are given in Table 4. Initial treatment consisted of prednisolone (2 mg/kg/day) and methotrexate in 47 (97.9%) and 46 (95.8%) patients, respectively. Furthermore, high-dose pulse corticosteroid therapy (30 mg/kg/day,

Table 5. Risk factors for the development of calcinosis

Parameter	Calcinosis		p
	Present	Absent	
Myalgia			0.003
Present	11	19	
Absent	0	18	
Livedo racemosa			0.049
Present	2	0	
Absent	9	37	
Skin hypopigmentation			<0.001
Present	6	0	
Absent	5	37	
Diagnostic delay, months	9.5 (1–48)	3 (1–24)	0.023
Physician VAS	8.0 (5.0–10)	6.0 (3–10)	0.006
ALT	41 (12–80)	73 (10–689)	0.026
Disease course, n (%)			
Monocyclic	4 (13.8)	25 (86.2)	0.003
Polycyclic	1 (14.3)	6 (83.7)	
Chronic persistent	6 (50.0)	6 (50.0)	

*: Categorical variables were compared with the Chi-square test or Fisher's exact test where appropriate. Mann–Whitney U-test was used to compare the continuous data between two groups. VAS: Visual Analog Scale; ALT: Alanine aminotransferase.

3 days) was given to 38 (79.2%) patients. The median duration of corticosteroid treatment was 14 (3–72) months. At the time of diagnosis, intravenous immunoglobulin was given to 15 (31.3%) patients and hydroxychloroquine was added to the regimen in 10 (20.8%) patients. Cyclosporine (2 patients) and cyclophosphamide (2 patients) were other medications that were used at the time of diagnosis. In 17 (35.4%) patients, treatment modifications were made during the disease course. The most commonly preferred second-line agent was mycophenolate mofetil. The mean time for disease remission in monocyclic patients was 2.2±1.3 months. In the last control, 35 patients (72.9%) were under remission, while 13 patients (27.1%) had active disease. Only 13 (27.1%) patients were off medication.

Complications were observed in 22 (45.8%) patients. The most common complications were corticosteroid-related (12 patients), including Cushing syndrome, osteoporosis, and hirsutism. Calcinosis was observed in 11 (22.9%) patients, most commonly in the form of local plaques. We also searched for risk factors for the development of calcinosis (Table 5). It was seen that myalgia, livedo racemosa, and skin hypopigmentation were more common in patients that developed calcinosis. Futhermore, there were statistically significant differences in the diagnostic delay, physician visual analog scale (VAS), and ALT levels at the time of diagnosis. Children with chronic persistent disease course had a higher rate of calcinosis. However, regression analysis showed that none of the above-mentioned parameters was an independent risk factor in predicting the development of calcinosis.

DISCUSSION

JDM is a rare disease with unpredictable outcomes. This study included six pediatric rheumatology centers in Turkiye with a relatively long duration of follow-up. It was seen that Gottron's papules, muscle weakness, and elevated muscle enzymes were observed in nearly all of the JDM cases. In this study, most of the JDM patients had a short time to be diagnosis after the first symptom and had a monocyclic course. However, the rate of calcinosis was similar to other studies.

JDM is reported from all over the world with the same female predominance and similar age at onset. Approximately two-thirds of JDM cases were female (61.9%–72%) in reports from all over the world. Moreover, the mean or median age at the onset of the disease was between 6 and 8 years [16–24]. Our JDM cohort had similar demographics and 68.8% of the cases were female and the mean age at disease onset was 7.6 years. Irrespective of country of origin, JDM seems to have a similar gender predominance and age of onset.

Skin involvement is the sine qua non in JDM. Typical skin rashes such as Gottron's papules and heliotrope rash are the main skin features that lead to considering JDM in the differential diagnosis list of an astute physician in children presenting with rash and weakness [1, 9, 14]. The largest JDM cohort, including 490 cases, reported the frequency of Gottron's papules and heliotrope rash as 72.9% and 62%, respectively [18]. Other studies reported much higher frequencies of these skin rashes. In a study from Australia, 91% had Gottron's papules and 73% had heliotrope rash [19]. Another study from Turkiye even reported higher frequencies, 96% for Gottron's papules and 100% for heliotrope rash [17]. Our study found similar results with the previous Turkish report, 97.9% of patients had Gottron's papules and 95.8% had the heliotrope rash.

The other cardinal feature of the disease is muscle involvement and it is clinically reflected as proximal muscle weakness. At one end, the weakness may be subtle and families or children may only complain of clumsiness. At the other severe end, the child may not be able to get off the bed. Proximal muscle weakness was observed in 99.7% of 354 JDM cases, and in 84.9% of 490 patients [2, 18]. The lowest ratio (74%) was reported by Sag et al. [16]. Proximal muscle weakness was observed in 89.6% of our patients.

Measurement of muscle enzymes is very helpful in establishing the diagnosis of JDM. An increase in any one of the five muscle enzymes, namely CK, AST, ALT, LDH, and aldolase, is observed in all JDM patients [2, 16–24]. Most of the studies reporting muscle enzyme abnormalities reported as elevated/normal and a few studies have given absolute numbers. Median CK and LDH levels were 337 U/L and 629 U/L in one study, while they were 829 U/L and 430 U/L in another study, respectively [2, 16]. The median levels of muscle enzymes in our cohort, especially of CK (1539 U/L), LDH (642 U/L), and AST (123) seem to be higher than in previous reports. This could be explained by the fact that our study did not include any children with amyopathic JDM and diagnosis was established within 3 months after the first symptom in the majority of the cases while they had the most intense muscle inflammation. Some JDM patients may have only one elevated muscle enzyme. In this study, it was seen that if only one enzyme is elevated, it was most commonly LDH, in agreement with another study [22]. Our study highlights that LDH may be more sensitive than CK in JDM, and we think that it should be ordered routinely in suspected JDM cases.

With the advent of MRI, the use of muscle biopsy has decreased dramatically in JDM cases [1, 4, 9, 14]. Muscle biopsy was performed in 52.8%, 48%, and 28% of the patients in three studies [17, 18, 24]. Gowdie et al. [19] reported diagnostic procedures in 57 patients that were diagnosed between 1989 and 2010. Twenty-eight patients were diagnosed after 2000, and they stated that MRI was performed in 86%, muscle biopsy in 14.2%, and EMG in none of the 28 patients. Muscle biopsy is more commonly performed in research centers to find prognostic factors related to the outcome, to enlighten the etiopathogenesis of the disease, and to be used in translational medicine [8, 9, 16]. MRI was performed in 75% and muscle biopsy in 35.4% of the patients in our study, but EMG was performed much higher (83.3%) than reported in the literature. EMG was chosen by the authors in most of the cases in this study because it is less invasive than muscle biopsy and gives valuable information with a short turnaround time.

Calcinosis is the main long-term complication and morbidity in JDM. It was reported in 12% to 47% of the patients [1, 2, 14]. Calcinosis was seen in 11 (22.9%) of the patients in our study, which stands neither high nor low according to the literature. The main risk factors are considered delay to diagnosis, older age at diagnosis, the duration of untreated active disease, and male gender [1, 14, 17, 25]. Some reports found that children diagnosed at a young age have a higher risk of calcinosis [16, 26]. Patwardhan et al. [21] compared the disease course and complication rates in 78 children with JDM. They grouped the cases by the onset of age; below 3 years of age (19 patients), and >3 years of age (59 patients). They found that calcinosis was more common in older children (22% vs. 15%). The definition of MSAs has led to a new era in the field of JDM. More and more studies have shown that we are close enough to define JDM subtypes based on the MSAs [2, 4, 8, 9, 16, 26–28]. From the point of calcinosis development, Anti-NXP2 (anti-MJ) is considered the major MSA subtype [9, 26, 28]. Unfortunately, we were not able to perform MSAs in all patients.

We have seen that calcinosis was more common in children with delay in diagnosis, and chronic persistent disease course. This again reminds us that the main risk factor for calcinosis is the duration of active disease, either secondary to late diagnosis or under treatment. The study of Kim et al. [12] emphasized the importance of early and aggressive treatment in JDM. With this treatment approach, they reported that persistent calcinosis was only seen in 12% of 49 patients. We can speculate that undertreatment may not be the cause of calcinosis in our cohort. We have also used an intensive treatment modality and corticosteroids and methotrexate were given to 97.9% and 95.8% of cases at the time of diagnosis, respectively. We have seen that the ratio of monocyclic disease course in our cohort was much higher (62.5%) and the chronic persistent course was lower (22.9%) than reported in the literature. Two large JDM studies, including 365 and 290 patients, reported the frequency of monocyclic course as 24.1% and 24.5%, and chronic persistent course as 52.3% and 50.3%, respectively [2, 28]. A high rate of monocyclic course and a relatively lower rate of calcinosis in our study may be explained by the early initiation of systemic corticosteroids and methotrexate. We have not found any significant as-

sociation of calcinosis with gender and age at onset of the disease, but we have seen that calcinosis was more common in children having myalgia, livedo racemosa, and skin hypopigmentation at the time of diagnosis. Another intriguing result was that patients with lower ALT levels at the time of diagnosis had a higher rate of calcinosis. Furthermore, physician VAS at diagnosis, but not the patient VAS, was higher in the calcinosis group. This could reflect a more objective view of a physician on the overall severity of JDM [29].

The review of Huber and Feldman gives us an understanding of how the prognosis and outcome of children with JDM have evolved since the early 1960s [30]. Once, the death rate was around 30%, and nowadays, it is less than 2%. Once one-third of children had serious functional complications; unfortunately, it is still the same. Even though we do not see those serious complications, long-term morbidities are still a major problem that faces children, families, and physicians [1, 14, 30]. Varnier et al. [31] reported a remission rate as 75% and a complication rate of 37.3% at 2 years. Mathiesen et al. [32] reported 13.9 years of follow-up results for 53 patients. They stated that 15.1% of patients still had active disease and 60.4% of the cohort had disease damage, cutaneous scarring being the most common (39.6%). At the time of enrollment, 72.9% had remission and 27.1% had active disease in our study. We have seen a similar ratio of complications (45.8%) related to disease or treatment. Most of the complications, such as hirsutism, Cushing syndrome, and osteoporosis, were related to chronic corticosteroid use. Persistent complications, such as muscle weakness, and skin atrophy/scarring, were seen in 16.6% and lipodystrophy in 6.2% of the patients, respectively.

The retrospective nature of the study is the major limitation of this study, but we have excluded patients with missing data. Another drawback of the study is that we were not able to perform MSAs and MAAs in all patients, and some patients had a follow-up duration of <2 years. Furthermore, we have looked at many factors to assess the risk of calcinosis, some may have been found incidentally. The inclusion of six centers from different parts of the country and the relatively long duration of follow-up seem to be the main strengths of our study.

Conclusions

JDM is a systemic lifelong disease with significant morbidities. In pediatric rheumatology, we develop classification and stratification systems to diagnose or predict the long-term prognosis in nearly every disease. However, some patients still defy our classification and long-term prediction algorithms. Even though we have made tremendous developments from the point of etiopathogenesis and treatment wise, the rate of calcinosis seems not to be decreasing compared to a few decades ago. The duration of active disease seems to be a major determinant for the development of calcinosis. We have also seen that calcinosis was more common in children having myalgia, livedo racemosa, skin hypopigmentation, lower alanine aminotransferase levels, and higher physician visual analog scores at the time of diagnosis.

Ethics Committee Approval: The Umraniye Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 29.04.2021, number: B.10.1.TKH.4.34.H.GP.0.01/124).

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