



BRIEF REPORT

Baseline Description of the Juvenile Localized Scleroderma Subgroup From the Childhood Arthritis and Rheumatology Research Alliance Legacy Registry

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Objective. Localized scleroderma (LS) is a chronic inflammatory and fibrosing skin disorder. We present baseline data on the juvenile LS (jLS) cohort from the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Legacy Registry, a multicenter observational registry of pediatric rheumatologic disorders.

Methods. This is a cross-sectional analysis of children with jLS enrolled in the CARRA Legacy Registry between May 2010 and April 2014. Descriptive statistics were used for demographic, clinical, and laboratory features. Data analysis included two-sample *t* test, χ^2 test, Fisher's exact test, linear/logistic regression, and analysis of variance.

Results. Of 381 children with jLS, 76% were female and 80% Caucasian. Mean onset age was 8.2 years, with 17% having a 2-year or greater delay to first pediatric rheumatology (PRH) visit. Linear scleroderma was the most common subtype (54%). Antinuclear antibody (ANA) positivity was associated with joint contracture ($P = 0.04$), muscle atrophy ($P = 0.014$), and extremity shortening ($P = 0.007$). Elevated aldolase was associated with joint contracture ($P = 0.008$) and elevated creatine kinase (CK) with muscle atrophy ($P = 0.028$) and extremity shortening ($P = 0.016$). Children with functional limitation (27%) had earlier first PRH visit compared with those without ($P = 0.01$). Poorer function correlated with muscle atrophy, joint contracture, and extremity shortening ($P < 0.001$). Methotrexate (97%) and corticosteroids (68%) were the most common medications used.

Conclusion. Children with jLS without joint limitation are referred later, highlighting the insidious onset and need for educating referring providers. Poorer function correlated with muscle atrophy, joint contracture, and limb shortening. ANA positivity and elevated CK or aldolase were associated with muscle atrophy, joint contracture, and/or limb shortening, suggesting predictors of muscle involvement.

INTRODUCTION

Juvenile localized scleroderma (jLS), also called “morphea,” is a chronic inflammatory and fibrosing skin disorder characterized by excessive collagen deposition (1,2). Juvenile LS has an estimated incidence of 3 cases per 100 000 children per year (3). The average age of disease onset is 7.3–8.3 years, and there is a slight female predominance with a reported

female:male ratio of 2.4:1 (4,5). The diagnosis of jLS is often delayed with a median time from disease onset to diagnosis of 11 to 13 months (6,7).

Localized scleroderma can be divided into five general subtypes: circumscribed morphea (superficial and deep), linear scleroderma (trunk/extremity and head), generalized morphea, pansclerotic morphea, and mixed subtype (8,9). Extent of disease involvement can vary and ranges from small, circumscribed

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SIGNIFICANCE & INNOVATIONS

- There is currently limited data on jLS from United States registries and only a few published series of children with jLS. We further contribute to the existing literature with the baseline data from a large prospective cohort of 381 North American children with jLS.
- Delay between jLS symptom onset and first PRH visit is not uncommon, highlighting the insidious nature of the disease and immense need to educate referring providers.
- Features of noncutaneous disease damage, including muscle atrophy, joint contracture, and extremity shortening, are common and can be associated with significant functional limitation. ANA positivity and elevated CK or aldolase may be possible predictors of noncutaneous disease damage.

plaques to extensive fibrotic lesions. In addition, involvement may extend beyond the skin to deeper subcutaneous tissue, muscles, joints, and even bone (10). Children with jLS may therefore develop severe deformities, including extremity length discrepancies, muscle atrophy, joint contractures, and facial atrophy. These sequelae are typically permanent and persist into adulthood (11). JLS is associated with considerable morbidity by causing substantial functional limitations and disability and having a negative impact on quality of life (12,13).

There is currently limited data on jLS from United States registries. In addition, there are only a few published series of children with jLS, each with a limited number of patients. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) is a North American organization of pediatric rheumatologists formed to facilitate high-quality research in the field of pediatric rheumatology. In 2009, CARRA created an observational registry to collect comprehensive information on all major pediatric rheumatic diseases and their treatments. The registry includes patients enrolled from 62 CARRA centers in North America. The objective of this study was to analyze the baseline enrollment data to describe the clinical features and patterns of care of the children with jLS in the CARRA Legacy Registry.

MATERIALS AND METHODS

Data source. The CARRA Legacy Registry is an observational longitudinal data capture study encompassing all major pediatric rheumatic diseases. Children were included in the analysis if they had a physician diagnosis of jLS and were enrolled into the CARRA Legacy Registry between May 2010 and April 2014. Patients were enrolled from 49 CARRA sites during this time period. Informed consent was obtained for all patients. During the baseline enrollment visit, demographic and disease-related data were collected from time of diagnosis to enrollment visit. Only data from each patient's enrollment visit were used for this analysis.

Institutional Board Review approval was obtained at each enrolling registry site.

Data collection. Sociodemographic and clinical data were collected from families and physicians using both general and jLS-specific case report forms at the time of enrollment. Subjects' medical records were also reviewed to obtain relevant disease-specific clinical information. Data were entered into and stored in a secure centralized electronic database. Data were deidentified prior to analysis. Children with any missing data were excluded from relevant analyses.

Disease activity was defined as presence of erythematous/violaceous color, lesion extension, skin induration at lesion perimeter, lesion warmth, and/or new lesion. Disease damage was defined as presence of hyperpigmentation, subcutaneous atrophy, dermal atrophy, hypopigmentation, lesional hair loss, muscle atrophy, joint contracture, extremity shortening, hemifacial atrophy, and/or skin thickening at lesion center. Extracutaneous manifestations were also collected and included hemifacial atrophy and any musculoskeletal, gastrointestinal, neurological, and ocular involvement. Specific focus on effects of the musculoskeletal system included arthritis, muscle atrophy, joint contracture, and extremity shortening. With the exception of arthritis, these musculoskeletal variables were also considered as noncutaneous disease damage. Extracutaneous and noncutaneous terminology refers to disease involving tissues other than the skin that can result from direct extension of a scleroderma lesion, or be remote from the lesion(s). Functional outcomes and quality of life measures were also collected. The American College of Rheumatology (ACR) 1991 criteria were used to assess global functional status, and presence of functional limitation was indicated by baseline worst ever ACR class II, class III, or class IV (14). The Patient Reported Outcome Measurement Information System (PROMIS) Pediatric Global Health (PGH-7) measure was used to rate overall health-related quality of life (15).

Statistical analyses. We computed means, SDs, frequencies, and proportions for all demographic, clinical, and laboratory features. Statistical analyses conducted included the two-sample *t* test, χ^2 test, Fisher's exact test, linear/logistic regression, and analysis of variance as appropriate. Patients with missing values were excluded from that particular analysis. As this was an exploratory analysis, the decision was made not to correct for multiple comparisons in order to identify all associations meriting further study. All computations were performed using Stata statistical software (Version 13.1, StataCorp LP). All tests were two-sided, and results were considered significant if $P < 0.05$. This study was reviewed and approved by the University of North Carolina at Chapel Hill's Institutional Review Board.

Table 1. Main demographic features of patients with juvenile localized scleroderma enrolled in the CARRA Legacy Registry

Feature	Overall	Linear	Mixed	Circumscribed	Generalized	Pansclerotic Eosinophilic Fasciitis
Patients (N, %)	381	207 (54.3%)	72 (18.9%)	60 (15.8%)	34 (8.9%)	8 (2.1%)
Gender (female:male)	3.1:1	2.6:1	2.8:1	5.7:1	5.8:1	3:1
Male (N, %)	94 (24.4%)	58 (28%)	19 (26.4%)	9 (15%)	5 (14.7%)	2 (25%)
Female (N, %)	292 (75.6%)	149 (72%)	53 (73.6%)	51 (85%)	29 (85.3%)	6 (75%)
Race/Ethnicity						
Caucasian	306 (80.3%)	168 (81.2%)	54 (75%)	49 (66.7%)	28 (82.4%)	7 (87.5%)
Hispanic	45 (11.8%)	22 (10.6%)	11 (15.2%)	8 (13.3%)	3 (8.8%)	1 (12.5%)
African American	8 (2.1%)	3 (1.4%)	3 (4.2%)	1 (1.7%)	1 (2.9%)	0 (0%)
Asian	7 (1.9%)	6 (2.9%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Other	15 (3.9%)	8 (3.9%)	3 (4.2%)	2 (3.3%)	2 (5.9%)	0 (0%)
Mean age at onset (year, SD)	8.2 (\pm 4.2)	7.9 (\pm 4.2)	8.3 (\pm 4.0)	9.2 (\pm 4.2)	8.1 (\pm 4.2)	7.7 (\pm 4.1)
Mean age at first evaluation with pediatric rheumatology (year, SD)	9.6 (\pm 4.1)	9.2 (\pm 4.1)	9.6 (\pm 3.8)	10.5 (\pm 4.2)	10.6 (\pm 4.2)	9.3 (\pm 3.5)
Family history of autoimmune disease (N, %)	91 (25.2%)	49 (25%)	11 (15.9%)	17 (29.3%)	12 (37.5%)	2 (33.3%)

RESULTS

Demographics. We identified 381 children with jLS with available baseline enrollment data. Important clinical characteristics of the patients are listed in Table 1. Of the 381 children in the database, 76% were female with a female:male ratio of 3.1:1. The majority of the children were Caucasian (80%). Mean age at symptom onset was 8.2 years (\pm 4.2, range 0-17 years). Mean age at first pediatric rheumatology evaluation was 9.6 years (\pm 4.1, range 0-20 years), and notably 17% had 2-year or longer delay from symptom onset to first pediatric rheumatology visit. There were no associations between jLS subtype and either age of symptom onset or duration of delay in diagnosis. As seen in other cohorts, a family history of autoimmunity was observed in approximately 25% of children with jLS, and generalized morphea subtype had the highest frequency (37.5%) (16). Among all subjects, the most common familial autoimmune disorders in decreasing frequency included autoimmune thyroid disease, psoriasis, type 1 diabetes mellitus, rheumatoid arthritis, celiac disease, Crohn's disease, and juvenile idiopathic arthritis.

Disease characteristics. Linear scleroderma was the most common subtype (54%), followed by mixed subtype (19%), circumscribed morphea (16%), generalized morphea (9%), and pansclerotic morphea and eosinophilic fasciitis (2%) (Table 1). Linear scleroderma with circumscribed morphea was the most frequent combination (61%) among those with mixed subtype. Among the linear scleroderma patients, 65% had lesions involving

the trunk and/or limbs. Among the 34% with face-scalp localization, neurologic and ocular diseases were reported in 11% and 4%, respectively. Neurologic and ocular involvement were only observed in the linear scleroderma subtype in our cohort. All patients with neurologic and 67% with ocular involvement had face or scalp lesions. Among the children with circumscribed morphea, 60% had superficial lesions only, 33% had deep lesions only, and 7% had superficial and deep lesions.

At baseline enrollment visit, 55% of children with jLS had one or more features of disease activity, and 94% of children had one or more features of disease damage. In addition, 46% of children with jLS had one or more extracutaneous disease manifestation, and 31% had one or more features of noncutaneous disease damage. Frequencies of extracutaneous disease damage were muscle atrophy 23%, joint contracture 18%, extremity shortening 9%, hemifacial atrophy 9%, and arthritis 5%. Neurologic, ocular, and gastrointestinal involvement were rare, occurring at frequencies of 3%, 2%, and 1%, respectively. Not all children had neurologic, ophthalmologic, or gastrointestinal assessments at enrollment, so these values may differ from the true frequency.

Laboratory parameters. Antinuclear antibody (ANA) positivity was found in 48% of the 296 subjects (78% of cohort) tested and was not associated with disease subtype or age at onset. ANA positivity, however, was associated with features of noncutaneous disease damage, specifically joint contracture (odds ratio [OR] 1.79 [95% confidence interval (CI) 1.03, 3.13]; $P = 0.04$), muscle atrophy (OR 2.02 [95% CI 1.15, 3.56]; $P = 0.014$), and extremity

shortening (OR 3.19 [95% CI 1.36, 7.47]; $P = 0.007$). Other pertinent laboratory findings included an elevated creatine kinase (CK) present in 21% of 237 subjects (62% of cohort) tested and an elevated aldolase in 14% of 196 (51% of cohort) tested. An elevated aldolase was associated with joint contracture (OR 3.13 [95% CI 1.34, 7.30]; $P = 0.008$), and elevated CK was associated with muscle atrophy (OR 2.78 [95% CI 1.12, 6.92]; $P = 0.028$) and extremity shortening (OR 3.64 [1.27, 10.45]; $P = 0.016$).

Functional outcomes and quality of life. A history of any functional limitation (ACR class II, III, or IV) was present in 27% of children with jLS. These children had an earlier first pediatric rheumatology evaluation (mean 0.98 year \pm 1.52) compared with those without any limitation (ACR class I) (mean 1.6 year \pm 2.2, $P = 0.01$). Poorer function also correlated with presence of muscle atrophy, joint contracture, and extremity shortening (all $P < 0.001$) (Figure 1). Children with a joint contracture tended to be referred sooner, with a 0.9-year earlier first pediatric rheumatology evaluation compared with those without joint contracture (95% CI $-1.50, -0.29$) ($P = 0.004$). Using the PROMIS PGH-7 measure, only 28% of children with jLS reported their health-related quality of life as excellent, with a majority reporting it as either very good (47%) or good (23%).

Treatment history. At baseline enrollment visit, 5% of children with jLS never received any systemic therapy. Approximately 67% of children with jLS were treated with either intravenous pulse or long-term daily corticosteroids (Table 2). Among those treated with corticosteroids, 97% received treatment with other immunosuppressants. Subcutaneous or oral methotrexate (97%) was the most common disease-modifying antirheumatic drug used, followed by mycophenolate mofetil (16%). Up to the time of enrollment, 76% of children with jLS received subcutaneous methotrexate and 58% received oral methotrexate. The only significant difference in treatment according to jLS subtype was the use of topical therapy instead of systemic therapy in superficial circumscribed

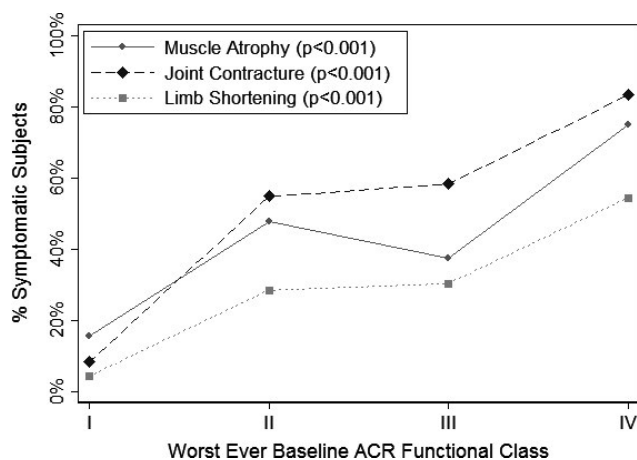


Figure 1. Poorer function is associated with muscle atrophy, joint contracture, and limb shortening.

morphea. Subjects with isolated superficial circumscribed morphea were 65% less likely to receive systemic corticosteroids compared with other subtypes (OR 0.35 [95% CI 0.20, 0.62]; $P < 0.001$).

DISCUSSION

In the CARRA Legacy Registry, jLS occurred more frequently in females and Caucasians. Linear scleroderma was the most common subtype, followed by mixed subtype and circumscribed morphea. Almost one-fifth of children with jLS had a 2-year or longer delay from symptom onset to first pediatric rheumatology visit. Although diagnosis by dermatology was not captured in this study, delays in diagnosis have been well described in prior cohorts with localized scleroderma diagnosed by both dermatologists and rheumatologists (17). Children without limitations were referred later, highlighting the insidious onset of the disease. The prolonged interval from disease onset to definitive diagnosis may adversely affect outcomes. Moreover, the delay underscores the need to raise awareness for this rare diagnosis and facilitate earlier recognition and referral to specialist services.

Children in the jLS cohort of the CARRA Legacy Registry had a high rate of extracutaneous manifestations, suggesting a need for earlier multisystem investigation and more aggressive treatment in those with widespread disease. In addition, jLS is associated with significant morbidity, with almost one-third of children reporting some degree of functional limitation. A history of functional limitation was associated with earlier pediatric rheumatology referral and evaluation as well as presence of muscle atrophy, joint contracture, and/or limb shortening. ANA positivity was comparable to prevalence rates previously reported (4,18). ANA positivity and elevations in CK or aldolase were associated with the presence of muscle atrophy, joint contracture, and/or limb shortening, and may be possible predictors of muscle involvement.

Our study does have several limitations. First, relying on retrospective data available through family recall or chart review may allow for inaccurate reporting, particularly for time of symptom onset and date of first pediatric rheumatology visit. Although our case report forms included multiple clinical features, with inclusion for skin activity and damage features, and extracutaneous and noncutaneous involvement, not all possible features were captured. As there are no biomarkers, all of these assessments were based upon the provider's clinical examination, and as only limited training and information were provided to participating sites, providers may have differed in the sensitivity of their assessments, so certain disease features may be underestimated. The jLS cohort of the CARRA Legacy Registry may also not represent the full disease spectrum. Only a subset of CARRA centers participated in the Legacy Registry, and because subjects were enrolled by pediatric rheumatologists, children with milder disease managed exclusively by pediatric dermatologists would not have been included. Those patients likely would have only been treated with topical therapies and/or phototherapy. ANA positivity

Table 2. Treatment history of children with juvenile localized scleroderma enrolled in the CARRA Legacy Registry

Medication	Overall	Linear	Mixed	Circumscribed	Generalized	Pansclerotic Eosinophilic Fasciitis
Oral methotrexate (N, %)	318	172	62	47	30	7
Current use	99 (31.1%)	50 (29.1%)	19 (30.6%)	19 (40.4%)	10 (33.3%)	1 (14.3%)
Prior use	87 (27.4%)	44 (25.6%)	24 (38.7%)	9 (19.2%)	8 (26.7%)	2 (28.6%)
Never use	132 (41.5%)	78 (45.3%)	19 (30.6%)	19 (40.4%)	12 (40%)	4 (57.1%)
Subcutaneous methotrexate (N, %)	319	174	62	46	30	7
Current use	138 (43.3%)	77 (44.3%)	28 (45.2%)	15 (32.6%)	14 (46.7%)	4 (57.1%)
Prior use	103 (32.3%)	61 (35%)	18 (29%)	16 (34.8%)	5 (16.7%)	3 (42.9%)
Never use	78 (24.4%)	36 (20.7%)	16 (25.8%)	15 (32.6%)	11 (36.6%)	0 (0%)
Mycophenolate mofetil (N, %)	319	173	62	47	30	7
Current use	41 (12.9%)	23 (13.3%)	9 (14.5%)	3 (6.4%)	4 (13.3%)	2 (28.6%)
Prior use	10 (3.1%)	5 (2.9%)	5 (8.1%)	0 (0%)	0 (0%)	0 (0%)
Never use	268 (84%)	145 (83.8%)	48 (77.4%)	44 (93.6%)	26 (86.7%)	5 (71.4%)
Intravenous corticosteroids (N, %)	257	143	53	28	26	7
Current use	34 (13.2%)	18 (12.6%)	8 (15.1%)	2 (7.1%)	2 (7.7%)	4 (57.1%)
Prior use	85 (33.1%)	52 (36.4%)	20 (37.7%)	2 (7.1%)	10 (38.5%)	1 (14.3)
Never use	138 (53.7%)	73 (51%)	25 (47.2%)	24 (85.7%)	14 (53.8%)	2 (28.6%)
Long-term daily corticosteroids (N, %)	254	140	53	28	26	7
Current use	66 (26%)	36 (25.7%)	16 (30.2%)	6 (21.4%)	6 (23.1%)	2 (28.6%)
Prior use	118 (46.4%)	59 (42.1%)	23 (43.4%)	16 (57.1%)	15 (57.7%)	5 (71.4%)
Never use	70 (27.6%)	45 (32.1%)	14 (26.4%)	6 (21.4%)	5 (19.2%)	0 (0%)

and elevated CK or aldolase may have been influenced by referral bias, so additional study is needed to assess their true prevalence and predictive value among children with localized scleroderma. Our analyses were not corrected for multiple comparisons and should therefore be considered hypothesis-generating.

Using the CARRA Legacy Registry, however, allowed us to evaluate a large North American cohort of children with jLS. Ours is also the second largest cohort of children with jLS published (4). Our study therefore further contributes to the existing literature of this rare disease and uncovers some important insights. Our study confirms prior observations that jLS is associated with significant disability, may have a negative impact on quality of life, and that there is often a delay between symptom onset and diagnosis (6,7,12,13,17). Our study also confirms prior observations that there is a high frequency of extracutaneous manifestations, particularly muscle atrophy, joint contracture, extremity shortening, and hemifacial atrophy, and that they are associated with significant functional limitations (10). The high frequency observed in our cohort emphasizes the need for a standardized approach for assessing and monitoring extracutaneous manifes-

tations in jLS, and standards of care are being developed (19). Our study is the first to highlight that ANA positivity and elevated CK or aldolase may be possible predictors of noncutaneous disease damage, specifically muscle atrophy, joint contracture, and/or limb shortening. Additional prospective, longitudinal research is needed to further study the observations made in this study.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Wu had full access to the all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Wu, Li, Torok, Virkud, Fuhlbrigge, Rabinovich.

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Analysis and interpretation of data. Wu, Li, Torok, Virkud, Fuhlbrigge, Rabinovich.

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APPENDIX 1

List of CARRA Legacy Registry Investigators:

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