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Predictors of Longitudinal Quality of Life in Pediatric Localized Scleroderma

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Abstract

Objective—Localized scleroderma (LS) can negatively affect children's quality of life (QoL), but predictors of impact are not well described. We sought to identify predictors of QoL impact in pediatric LS patients.

Methods—We analyzed longitudinal data from a single-center cohort of pediatric LS patients, using hierarchical generalized linear modeling (HGLM) to identify predictors of QoL impact. HGLM is useful for nested data and allows for evaluation of both time-variant and time-invariant predictors.

Results—The number of extracutaneous manifestations (ECMs) (e.g. joint contracture, hemifacial atrophy) and female gender predicted negative QoL impact, defined as Children's Dermatology Life Quality Index (CDLQI) score > 1 ($p = 0.019$, $p = 0.002$ respectively). As time from initial visit increased, the odds of reporting negative QoL impact decreased ($p < 0.001$).

Conclusion—Our results suggest that ECMs, gender, and time from initial visit are more predictive of QoL impact in LS than cutaneous features. Further study is required to determine which ECMs have the most impact on QoL, which factors underlie gender differences in QoL in LS, and why increasing time from initial visit appears to be protective. Improved understanding of predictors of QoL impact may allow for identification of patients at risk of poorer outcomes and tailoring of treatment and psychosocial support.

Pediatric localized scleroderma (LS), also known as morphea, is an autoimmune disorder of skin and underlying tissue that causes progressive fibrosis and atrophy. LS can cause disfigurement and functional limitation of involved joints (1). Affected children may develop extracutaneous manifestations (ECMs), e.g. arthritis, uveitis, gastrointestinal dysmotility, and neurological abnormalities (2). Surprisingly, studies on quality of life (QoL) in LS have revealed only modest impact (3–6). However, these studies were limited by cross-sectional designs, underrepresentation of some disease subtypes, absence of validated disease severity measures, and limited information regarding ECMs. Further, the studies were not designed to determine what factors predict QoL impact.

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Understanding predictors of QoL impact may help identify LS patients at highest risk for poor QoL, with medical and psychosocial interventions tailored accordingly. The aim of this study was to conduct a longitudinal analysis of predictors of QoL impact in LS. We analyzed data from the National Registry for Childhood Onset Scleroderma (NRCOS), a single center registry prospectively collecting detailed clinical, treatment, and QoL data. This unique resource allowed this longitudinal study to incorporate a wide variety of potential predictors of QoL.

PATIENTS AND METHODS

Study Design

We conducted a retrospective cohort study to identify predictors of longitudinal QoL impact in children with LS. The University of Pittsburgh institutional review board approved the NRCOS cohort study from which data herein were derived. Written consent was obtained for all participants and the study complied with the Declaration of Helsinki.

Participants

The NRCOS cohort received IRB approval in 2003 and enrollment remains open. Patients were recruited into NRCOS from the Pediatric Scleroderma Clinic at the Children's Hospital of Pittsburgh of UPMC. All patients were diagnosed by a pediatric rheumatologist, with disease subtype designated using Padua criteria. Data analyzed in this study was limited to 4–16 year old participants seen from October 2007 through August 2013 because QoL data has been gathered in NRCOS since 2007 using a QoL instrument (see 'Variables' below) that was validated specifically for this age range (7).

Variables

Primary Outcome – Quality of Life Variable—QoL was measured using the Children's Dermatology Life Quality Index (CDLQI). The CDLQI was selected because it has been extensively validated in diverse pediatric inflammatory skin diseases (e.g. eczema, psoriasis) and has been used most frequently in prior LS studies (4–7). CDLQI ranges from 0 to 30, with higher scores indicating worse QoL. Because CDLQI data were highly skewed (i.e. majority of scores in lower range), we dichotomized the variable. Scores of 0–1 indicate absence of QoL impact, and > 1 indicate presence of QoL impact; this definition was based on previously established score ranges (6,8).

Demographic/Clinical Variables—We assessed demographic/clinical variables including gender, race/ethnicity, age at initial diagnosis and enrollment visit, disease subtype, and number of affected body sites. Lesion location and subtype were operationalized as presence/absence of facial involvement and linear limb/trunk lesions respectively. The Localized Scleroderma Cutaneous Assessment Tool (LoSCAT) was used to quantify severity of skin disease. The LoSCAT is a validated measure that includes the modified Localized Scleroderma Skin Index (mLoSSI) and the Localized Scleroderma Damage Index (LoSDI), which assess cutaneous disease activity/damage respectively (9,10). Physician-documented disease state (i.e. active/inactive/flare) at each study visit was also obtained.

ECMs are documented prospectively and longitudinally by the NRCOS primary investigator (KT) at each study visit using standardized clinical research forms. The forms include a comprehensive ECM list based on literature review, requiring the physician to document if ECMs are specifically attributable to LS (versus medication side effects or other comorbidities)(2). ECM data were extracted from NRCOS, reviewed by study team for accuracy, and used to create counts of the total number of ECMs ever experienced by each patient.

Treatment Variables—Data were extracted denoting if patients were on/off systemic immunosuppressive treatment at each study visit. The number of medication side effects at each visit was also documented. Systemic therapy typically consisted of subcutaneous methotrexate and oral steroids as previously published, and treatment was tapered based on achievement of inactive cutaneous disease (e.g. mLoSSI = 0) rather than cutaneous damage (e.g. LoSDI) or ECMs (11).

Statistical Analysis

Hierarchical generalized linear modeling (HGLM) with logit link function was used to determine predictors of QoL impact (i.e. CDLQI score > 1). HGLM is an extension of hierarchical linear modeling, allowing for correlated error terms in multi-level data. We used HGLM because our data were longitudinal with multiple observations nested within each subject. In addition to the flexible error structure, HGLM allowed examination of predictors that were time-variant (i.e. on/off systemic treatment, which varies at each study visit) and time-invariant (i.e. stable characteristics like gender) on a binary outcome. Because the data are longitudinal, ‘time’ was included in the null model and the functional form examined. Time was defined in months from the initial visit to the clinical visit. Data cleaning and modeling were done respectively using IBM SPSS Statistics (version 20) and HLM 7 Student Version (SSI: Scientific Software International, Hierarchical Linear & Non Linear Modeling).

Model Building—Predictor variables were assessed univariably (modified alpha level = 0.10), and all statistically significant variables were included in the final multivariable model (alpha = 0.05). Robust standard errors were used. Non-significant variance components were removed from the final model; both unit-specific and population-average results were compared.

RESULTS

Patient Demographic/Clinical Features

Eighty subjects (616 visits) were included in the analysis, for a median 29.5 months follow-up (IQR: 14.0–50.3 months; average 6–7 visits). Table 1 summarizes demographic/clinical features, which were representative of LS populations (1). Median patient age was 7.8 years at disease onset (IQR: 4.9–10.3 years) and 10.4 years (IQR: 8.0–13.2 years) at initial NRCOS study visit. Two-thirds of participants reported at least one ECM at any visit. Table 2 lists ECMs by organ system in order of prevalence. Musculoskeletal, orofacial, and neurological ECMs were most common.

Visit descriptive statistics were examined. Patients were on systemic immunosuppressive therapy 68% (n=420) of study visits, with medication side effects reported at 55% (n=337) of study visits. LS disease state was assessed at the majority of visits, with inactive disease at 78% (n=480) of visits, active disease at 17% (n=106) of visits, and 5% (n=30) of visits not documented. Among visits with active disease documented, 25% (n=26) of those were considered to be disease flares.

For all visits, the raw CDLQI scores were not normally distributed (median: 1; IQR: 0–4; range: 0–17), in accord with previously published CDLQI scores in pediatric LS (4–6). Patients reported QoL impact most frequently on items assessing negative emotional responses due to their skin (item 2, 40% > 0), treatment burden (item 10, 40% > 0), and presence of itch or pain (item 1, 28% > 0). CDLQI total score > 1, denoting the presence of QoL impact, was seen at 49% (n = 299) of visits.

Model Building

Time was treated as linear in all subsequent models as the quadratic form of the variable was not significant ($p = 0.183$). Univariable significant variables included time from initial visit, gender, mLoSSI, LoSDI, and number of ECMs (Table 3), and these were all included in the final multivariable model (Table 3). Gender, number of ECMs ever experienced, and time from initial visit remained significant in both unit-specific and population-average models ($p < 0.05$). Males were less likely to report QoL impact than females ($OR: 0.12$, $p = 0.002$, $95\% CI: 0.03–0.44$). Each additional ECM increased the likelihood of QoL impact by 37% ($OR: 1.37$, $p = 0.019$, $95\% CI: 1.05–1.77$). Each month after the initial visit yielded 5% lower odds of QoL impact ($OR: 0.95$, $p < 0.001$, $95\% CI: 0.93–0.97$). Incremental increases in LoSDI scores predicted higher odds of QoL impact in the unit-specific model ($OR: 1.04$, $p = 0.024$, $95\% CI: 1.01–1.07$), but the result did not reach statistical significance in the population-average model ($p = 0.131$). mLoSSI scores failed to reach significance in either multivariable model.

DISCUSSION

Pediatric LS is an uncommon skin condition whose impact on QoL remains incompletely understood, with prior studies limited by cross-sectional designs (3–6). To our knowledge, this study is the first longitudinal assessment of predictors of QoL impact in LS. We found the number of ECMs a patient has ever experienced, their gender, and time from their initial visit significantly predict QoL impact.

Previous studies have not found associations between CDLQI scores and disease subtype, lesion location, number of affected body sites, or physician-scored LS cutaneous severity (6). As in prior studies, cutaneous activity and damage did not consistently reach statistical significance in our multivariable models. However, examination of the impact of ECMs on QoL has been limited to date (3–6). Longitudinal, prospective, and standardized documentation of ECMs in NRCOS allowed for more detailed examination of impact on QoL in this cohort. We found the odds of adverse QoL impact increased with each ECM reported in a patient's course, suggesting that ECMs exert an important and previously underappreciated impact on QoL. For example, musculoskeletal ECMs such as joint

contractures were commonly noted in our study population and may negatively impact QoL due to functional limitations. A wide variety of other ECMs were also noted in our study (Table 2), with potential for diverse detrimental effects on QoL.

Female participants had increased odds of reporting adverse QoL impact. One prior study of LS reported mixed results on the association of gender and QoL, with male pediatric patients and female adult LS patients having worse QoL (6). While our study was not designed to determine underlying reasons for gender differences, we examined descriptive statistics post hoc by gender. There were no gender differences in disease activity (i.e. mLoSSI), damage (i.e. LoSDI), rates of disease flare, number of affected body sites, lesion location, total number of ECMs, types of ECMs reported, or average numbers of treatment side effects (data not shown). However, female patients had a trend toward later mean age of symptom onset (8.1 vs. 6.5 years, $p = 0.076$, chi-square test) and significantly different age at diagnosis (10.1 vs. 8.2 years, $p = 0.013$, chi-square test). Yet, time from symptom onset to diagnosis did not differ between females and males (23.3 vs. 19.7 months, $p = 0.651$, Mann-Whitney U test). Older age at onset has reportedly been associated with higher rates of disease relapse, implying more severe disease phenotypes (12). We also noted post hoc that females were on systemic immunosuppressive treatment at fewer study visits than males (66% vs. 74% of visits), suggesting potential treatment variations by gender. Differences in coping techniques, family dynamics, situational anxiety, and rates of psychological distress could affect female LS patients' QoL (13,14).

We also found the odds of QoL impact decrease with time from initial visit. A possible inverse association between LS disease duration and QoL has been previously suggested (6). While we could not directly determine underlying reasons for this relationship, effective multimodal treatment combining immunosuppressive medications with physical and occupational therapy could lead to a decreased likelihood of QoL impact. Psychosocial factors such as development of child and family coping skills may also be important contributors in the long-term decrease of QoL impact. Future studies should examine these factors in detail.

This study has a few limitations. First, owing to the relative rarity of LS, the total number of participants in our study was small, limiting statistical power. However, our sample size was comparable to prior studies, a large number of study visits was included, median follow-up was greater than 2 years, and all major disease subtypes were proportionally represented (1,3–6). Because ECMs were diverse but often present in low numbers in our sample, we could not analyze whether specific subsets of ECMs conferred different odds of QoL impact. Given that the CDLQI item for treatment burden frequently revealed adverse impact yet neither the use of systemic therapy nor the number of medication side effects were strong predictors of QoL impact, future studies should consider using qualitative methods and/or newly validated instruments to assess side effects of immunosuppressive medications as this may increase precise quantitation of specific treatment burden domains and resulting QoL impact (15). Likewise, the CDLQI item assessing skin symptoms (e.g. itchy, scratchy, sore) often captured adverse impact but physician-scored cutaneous severity (i.e. mLoSSI, LoSDI) did not strongly predict QoL impact in our model, suggesting skin scores may be inadequate

proxies for uncomfortable skin symptoms. Future studies should directly assess pruritus and other LS skin symptoms' potential associations with QoL (6).

The single center study design could theoretically limit generalizability, particularly given that patients are evaluated at a clinic devoted specifically to LS. However, the study site serves a large catchment area reaching into multiple adjacent states as well as nationally referred patients and this is reflected in the representative sample described here (Table 1). Furthermore, while this study was conducted via a specific clinic devoted to LS patients, this clinic is staffed solely by the treating pediatric rheumatologist as would be the case at other sites, so the findings remain broadly applicable to LS patients seen in most pediatric rheumatology clinics.

Finally, the dichotomization of the CDLQI scores may limit the ability to quantify exactly how much each predictor variable affects QoL. While some information is lost with this approach, dichotomizing the study outcome allowed for use of HGLM, with this advanced statistical technique affording multiple strengths including the ability to include all study visits (as opposed to analyzing multiple time points cross-sectionally), incorporation of both time-variant and -invariant variables, and the ability to account for the repeated measures structure of the data. While the study findings and approach may be novel, they nevertheless represent only an initial step in the study of longitudinal QoL in LS patients with much further work remaining in this area.

Our findings have important implications for clinical practice and future research. Increased attention may need to be paid to gender differences in the impact of LS on patients, and approaches to psychosocial support may need to be tailored to boys and girls. We also found that extracutaneous manifestations of LS strongly predicted QoL impact. Thus, we should regard LS as a multisystem disease exerting serious effects on quality of life through musculoskeletal limitation and other organ manifestations. Future studies should clarify which ECMs are most consequential, directing treatment accordingly. The relationship between time from initial visit and QoL should be explored further in order to determine the factors underlying this protective effect and, if possible, intervene via improved biomedical treatment, physical/occupational therapy, or psychosocial supports. Continued recognition of predictors of QoL impact in LS may facilitate identification of high-risk patients and targeted interventions to meet these patients' needs.

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SIGNIFICANCE AND INNOVATIONS

- Predictors of quality of life in localized scleroderma are poorly understood.
- Extracutaneous manifestations, gender, and time from initial visit predict quality of life (QoL) impact in pediatric localized scleroderma.
- Localized scleroderma cutaneous features have limited ability to predict QoL in affected children.
- Further study is indicated to better understand how localized scleroderma affects QoL and to determine strategies for improving QoL in affected children.

Table 1

Participant Characteristics (n=80 Pediatric Localized Scleroderma Patients)

Female Sex , n (%)	58 (73%)
Race (White) , n (%)	74 (93%)
Age at Disease Onset (years), Median (IQR)	7.8 (4.9 – 10.3)
Age at Diagnosis (years), Median (IQR)	9.5 (7.2 – 11.9)
Age at Initial Study Visit (years), Median (IQR)	10.4 (8.0 – 13.2)
Disease Subtype , n (%)	
Linear (limb/trunk)	26 (32.5%)
En Coup De Sabre/Parry-Romberg	14 (17.5%)
Generalized Morphea	10 (12.5%)
Superficial Circumscribed	8 (10%)
Deep Circumscribed	4 (5%)
Mixed Subtype	18 (22.5%)
Lesion Location , n (%)	
Face/Neck Lesion Present	28 (35%)
Trunk Lesion Present	43 (54%)
Limb Lesion Present	50 (63%)
Subjects with 1 ECM , n (%)	53 (66%)
Median ECMs (IQR)	1.5 (0–3)

IQR: Interquartile Range; ECM: Extracutaneous Manifestation

Table 2

Prevalence of Extracutaneous Manifestations (ECMs) by Organ System *

	n (%)
Musculoskeletal	39 (49%)
Arthralgia	26 (33%)
Joint Contracture	21 (26%)
Limb Circumference Discrepancy	18 (23%)
Limb Length Discrepancy	6 (8%)
Myalgia	5 (6%)
Arthritis	4 (5%)
Gait Abnormality	4 (5%)
Orofacial	18 (23%)
Hemifacial Atrophy	18 (23%)
Dental Problems	10 (13%)
Tongue Atrophy	3 (4%)
Neurologic	15 (19%)
Headache	12 (15%)
Peripheral Neuropathy	3 (4%)
MRI Abnormalities (Brain)	3 (4%)
Ocular	6 (8%)
Dry Eye	3 (4%)
Gastrointestinal	3 (4%)
Dysphagia or Esophageal Dysmotility	3 (4%)
Vascular (i.e. Raynaud's Phenomenon)	4 (5%)

* Participants may have more than one ECM in a given category

ECMs present in n < 3 participants as follows: Myositis (n = 2); Muscle Weakness (n = 2); Back Pain Due to Leg Length Discrepancy (n = 1); Cramping (n = 1); Temporomandibular Joint Involvement (n = 1); Tongue Spasm (n = 1); Bell's Palsy (n = 1); Ataxia (n = 1); Dysarthria (n = 1); Cognitive Dysfunction (n = 1); Intention Tremor (n = 1); Episcleritis/Scleritis (n = 2); Pseudopapilledema with Optic Nerve Thickening (n = 1); Constipation (n = 1); Abdominal Pain (n = 1); Dry Mouth (n = 2); Fatigue (n = 2); Nephritis (n = 1); Pressure Sores Due to Contracture (n = 1); Erythema Nodosum (n = 1).

Table 3

Univariable and Multivariable Longitudinal Models of Quality of Life Impact

Univariable Model (modified alpha = 0.1):			
	Odds Ratio	95% CI	p-value
Time (months from initial visit)	0.95	(0.93, 0.97)	<0.001
Male Gender	0.14	(0.04, 0.49)	0.003
mLoSSI	1.14	(1.03, 1.25)	0.009
LoSDI	1.04	(1.01, 1.09)	0.008
# ECMs Ever Experienced	1.40	(1.08, 1.83)	0.013
Age at Diagnosis	1.61	(0.72, 3.61)	0.241
Facial Lesion Present	1.25	(0.35, 4.58)	0.725
Linear Limb/Trunk Lesion Present	1.72	(0.55, 5.41)	0.349
# Body Sites Affected	1.15	(0.95, 1.40)	0.155
Flare at Visit	0.65	(0.23, 1.87)	0.422
Systemic Immunosuppressive Treatment	0.79	(0.49, 1.28)	0.326
# of Side Effects at Visit	1.11	(0.87, 1.42)	0.387
Multivariable Model (alpha = 0.05):			
Time (months from initial visit)	0.95	(0.93, 0.97)	< 0.001
Male Gender	0.12	(0.03, 0.44)	0.002
mLoSSI	1.09	(0.97, 1.23)	0.148
LoSDI *	1.04	(1.01, 1.07)	0.024
# ECMs Ever Experienced	1.37	(1.05, 1.77)	0.019

Unit-specific model results shown. Bold results are statistically significant in both unit-specific and population-average models.

* not statistically significant in population-average model ($p = 0.131$, not shown)

mLoSSI: Modified Localized Scleroderma Skin Index

LoSDI: Localized Scleroderma Damage Index

ECM: Extracutaneous Manifestation