Measuring the Effect of Cutaneous Neurofibromas on Quality of Life in Neurofibromatosis Type 1

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Abstract

Objective

In order to explore the use of Skindex scoring in patients with neurofibromatosis type 1 (NF1) across multiple clinical sites and inform design of additional quality of life measures, we analyzed correlations between Skindex, site, and clinical measures for 79 patients with NF1 from specialized clinics in Sydney, Australia (Royal North Shore Hospital [RNS]) and Minneapolis, Minnesota (University of Minnesota [UMN]).

Methods

The relationship between clinical factors and Skindex scores were explored by clinic site and overall.

Results

A total of 40 participants were recruited from RNS and 39 from UMN. Female sex, total number of cutaneous neurofibroma (cNF), and whether cNF were present on the face correlated highly with Skindex and not Riccardi scores. The UMN site had lower average scores, but these differences were almost entirely removed after adjusting for age, sex, facial cNF, and total cNF number.

Conclusions

The development of cNF in adolescence and adulthood in NF1 often leads to progressive disfigurement and discomfort and is among one of the most common reasons for patients to seek medical treatment. Skindex has been used to assess skin-related quality of life in NF1 previously but is not specific to NF1. These findings highlight the need for a low threshold for referral to dermatologists for all patients with NF1 regardless of the severity of disease. The finding that facial cNF and higher total number of cNF correlates with poorer skin-related quality of life may benefit design of more specific NF1 skin-related quality of life measures.

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Glossary

cNF = cutaneous neurofibroma; NF1 = neurofibromatosis type 1; QoL = quality of life; RNS = Royal North Shore Hospital; UMN = University of Minnesota.

Neurofibromatosis type 1 (NF1) is a rare progressive multi-system genetic disorder of tumor susceptibility.^{1,2} Patients are predisposed to benign and malignant tumors of the peripheral nervous system and CNS, breast, thyroid, and adrenal gland.¹ NF1 is highly variable. Potential complications include disfiguring and disabling plexiform neurofibromas, orthopedic abnormalities, autism, and variable learning disability.^{2,3} Patients may experience minimal effect on their functioning, whereas others struggle with significant burden and overall reduction in health-related quality of life (QoL).⁴⁻⁸ Patients with more visible NF1 manifestations report greater reduction in QoL than those with less visible manifestations.⁹⁻¹¹

Most people with NF1 will develop cutaneous neurofibroma (cNF) by age 30.¹² The number and volume of cNF increase with age, but may vary in different regions of the body.^{13,14} The average number of cNF has been seen to increase from approximately 10 under the age of 10 to over 1,000 from the 40th decade onward.^{9,14} Although the number of neurofibromas may vary widely between patients, and within families, most are on the trunk (60%), with approximately 10% on the head and neck.^{13,14} cNF often lead to progressive disfigurement and discomfort for affected patients, and are among one of the most common reasons for patients to seek medical treatment.^{14,15}

Table 1 Demographic and Clinical Characteristics

Measure	Overall (n = 79)	RNS (n = 40)	UMN (n = 39)	p Value
Total Skindex-29	30.7 (25.9)	38.8 (25.6)	22.4 (23.9)	0.004 ^a
Physical/symptoms	31.1 (24.0)	37.1 (24.6)	24.9 (21.9)	0.022 ^a
Emotions	39.7 (32.6)	51.6 (32.2)	27.4 (28.4)	<0.001 ^a
Functional	21.5 (25.0)	26.7 (25.0)	16.2 (24.1)	0.060
Itch question	53.2 (32.9)	57.5 (33.6)	48.7 (31.9)	0.237
Age, y	38.7 (12.7)	40.7 (12.4)	36.7 (12.8)	0.159
Male, n (%)	32 (40.5)	15 (37.5)	17 (43.6)	0.650
Cutaneous NFs, n (%)				0.012 ^a
0	6 (7.6)	0 (0)	6 (15.4)	
1-19	15 (19.0)	6 (15)	9 (23.1)	
20-99	17 (21.5)	11 (27.5)	6 (15.4)	
100-500	11 (13.9)	2 (5.0)	9 (23.1)	
>500	29 (36.7)	20 (50.0)	9 (23.1)	
Missing	1 (1.3)	1 (2.5)	0 (0)	
Face, n (%)	41 (52)	18 (45)	23 (59)	0.365
Riccardi, n (%)				0.010 ^a
Minimal	2 (2.5)	1 (2.5)	1 (2.6)	
Mild	16 (20.3)	14 (35)	1 (5.1)	
Moderate	41 (52)	18 (45)	23 (59.0)	
Severe	18 (22.8)	7 (17.5)	11 (28.2)	
Missing	2 (2.5)	0 (0)	2 (5.1)	

Abbreviations: NF = neurofibromatosis; RNS = Royal North Shore Hospital; UMN = University of Minnesota.

Continuous measures were summarized using mean (SD) and compared with the 2-sample *t* test. The *p* values for the binary categorical variables (sex, face) are from the Fisher exact test. The *p* values for the ordinal variables (number of cutaneous NFs, Riccardi) are from the nonparametric Mann-Whitney *U* test.

^a Significant at *p* < 0.05 level.

Table 2 Relationship Between Clinical Factors and Skindex Scores for all Domains and by Site

Both sites	Total skindex		Physical		Emotions		Functional	
	Statistic	p Value	Statistic	p Value	Statistic	p Value	Statistic	p Value
Age, r	0.13	0.242	0.24	0.035	0.08	0.51	0.11	0.333
Sex, mean	F: 37.8	0.001	F: 36.3	0.016	F: 48.8	0.001	F: 27.8	0.002
Number of cNF, r _s	0.50	<0.001	0.46	<0.001	0.46	<0.001	0.48	<0.001
Facial NF, mean	Y: 38.9	0.002	Y: 38.0	0.007	Y: 48.0	0.015	Y: 29.2	0.003
Riccardi score, r _s	-0.10	0.371	0.00	0.994	-0.16	0.157	-0.05	0.696
UMN								
Age, r	0.19	0.258	0.32	0.044	0.12	0.479	0.14	0.409
Sex, mean	F: 28.0	0.078	F: 30.7	0.049	F: 34.0	0.089	F: 20.5	0.170
Number of cNF, r _s	0.63	<0.001	0.46	0.003	0.62	<0.001	0.60	<0.001
Facial NF, mean	Y: 32.9	<0.001	Y: 30.7	0.035	Y: 41.1	<0.001	Y: 26.0	<0.001
Riccardi score, r _s	0.06	0.713	0.05	0.760	0.05	0.779	0.16	0.354
RNS								
Age, r	0.00	0.985	0.10	0.533	-0.07	0.662	0.02	0.883
Sex, mean	F: 46.4	0.015	F: 41.1	0.177	F: 61.9	0.010	F: 34.3	0.008
Number of cNF, r _s	0.28	0.083	0.36	0.024	0.17	0.308	0.26	0.112
Facial NF, mean	Y: 46.5	0.095	Y: 47.2	0.021	Y: 56.8	0.357	Y: 33.3	0.140
Riccardi score, r _s	-0.06	0.725	0.05	0.761	-0.14	0.376	-0.07	0.667

Abbreviations: cNF = cutaneous neurofibroma; NF = neurofibromatosis; RNS = Royal North Shore Hospital; UMN = University of Minnesota.

Age is summarized by Pearson correlation. Sex and facial NF are summarized by means and tested by *t* test. Riccardi score and number of NF are tested by nonparametric Spearman correlation.

This study presents correlations between Skindex and clinical characteristics collected from clinics in Sydney, Australia, and Minneapolis, Minnesota. The feasibility of combining data across sites with different clinical characteristics and demographics is examined.

Methods

Participants, Standard Protocol Approvals, Registrations, and Patient Consents

Patients attending an NF1 skin clinic at Royal North Shore Hospital (RNS) or an NF1 clinic from the University of Minnesota (UMN) were invited to participate. At RNS, the primary focus is treatment of cutaneous manifestations of NF1 in patients over the age of 18; at UMN, the clinic focuses on general management and care. Before participation, all patients provided written informed consent. The Human Research Ethics Committees of RNS and the UMN approved the protocol (LNR/15/HAWKE/360; STUDY00001191). All study information was collected at a single patient visit.

Survey Instrument

Participants were asked to complete the paper form of the Skindex-29 questionnaire.^{16,17} Skindex-29 is one of the most

commonly used dermatology-specific QoL instruments. Skindex-29 responds to change over time and has been used in clinical trials in several diseases.^{18,19} This instrument includes 29 questions that assess the physical (7 question), emotional (10 questions), and functional (11 questions) effects of skin conditions; there is one additional question to assess itch. The response to each question on the Skindex was coded (0 = never; 25 = rarely; 50 = sometimes; 75 = often; 100 = all the time).

Clinical Assessment

cNF were assessed by the treating physician. The number of cNF (0, 1–19, 20–99, 100–500, or >500), presence or absence of cNF on the face, and Riccardi score²⁰ of severity were collected. The Riccardi NF1 severity scale ranges from levels 1 to 4, where level 1, minimal NF1, is the presence of few features; level 2, mild NF1, involves enough stigmata to make the disease obvious but with no compromise of health; level 3, moderate NF1, is associated with significant but well-managed compromise of health; and level 4, severe NF1, has serious intractable compromise of health, managed or treated with difficulty.

Statistical Considerations

Patient demographics, other relevant clinical information, and Skindex total score and subdomain score (physical, emotions,

Figure Skindex Comparisons by Site, Cutaneous Neurofibroma (cNF) Number, and Location

function, and itch) were summarized descriptively. Comparisons between sites were made using 2-sample t tests for continuous measures, Fisher exact tests for binary measures, or Mann-Whitney U test for ordinal measures. The relationship between the clinical factors and Skindex scores was

explored by clinic site and overall for each of the Skindex subdomains. Pearson correlation was used to summarize the numeric measures. Spearman correlation was used for ordinal measures and means and t tests were used for binary measures.

Table 3 Linear Regression of Site-Related Differences

Skindex measure	Unadjusted average difference and 95% CI (UMN – RNS)	Unadjusted p value	Adjusted average difference and 95% CI (UMN – RNS)	Adjusted p value
Total	–16.4 (–27.5, –5.3)	0.004	–11.6 (–24.7, 1.5)	0.081
Physical	–12.2 (–22.7, –1.8)	0.022	–8.0 (–21.2, 5.2)	0.230
Emotions	–24.2 (–37.8, –10.5)	<0.001	–16.8 (–32.5, –1.2)	0.036
Functional	–10.5 (–21.5, 0.5)	0.060	–7.2 (–20.7, 6.3)	0.292
Itch question	–8.8 (–23.5, 5.9)	0.237	–2.8 (–22.2, 16.7)	0.776

Abbreviations: CI = confidence interval; RNS = Royal North Shore Hospital; UMN = University of Minnesota.

The average site difference (UMN – RNS), 95% CI, and p value for each Skindex measure from the simple linear regression model (unadjusted), as well as the multiple linear regression model (adjusted for age, sex, the numbers of NFs, whether NFs were present of the face, and Riccardi score).

To account for possible confounding, we used multiple linear regression models to assess whether the average Skindex score differed by site after adjusting for differences in age, sex, the number of cNF, whether cNF were present on the face, and Riccardi score. Separate models were run for the total average score and each subdomain (physical, emotions, functional, itch). The relative importance of each covariate in the regression models was calculated by the *relatimpo* package in R (V.2.2), which averages over orderings of sequential R².²¹ Each covariate in the model has a relative importance score between 0 and 1, where values closer to 1 represent a larger contribution to the model and the sum of all the scores in the model add up to 1. There are no guidelines for what cutoff constitutes a high relative importance, as that depends on the specific context of the analysis and the number of covariates in the model.

To assess whether the relationship between the total average Skindex score and the clinical measures significantly differed by site, the interactions between site and the clinical measure were separately tested in a regression model, with only the interaction and main effects of site and the clinical measure as covariates. Analyses were conducted in R version 3.5.1. *p* Values less than 0.05 were considered statistically significant.

Data Availability

Any data not published within this article are available in a public repository.

Results

A total of 79 patients completed the Skindex survey: 40 from RNS and 39 from UMN. Participant demographics are shown in table 1. Patients from the UMN site were slightly younger on average (36.7 [12.8] vs 40.7 [12.4]), more likely to be male (44% vs 38%), and more likely to have facial cNF (59% vs 45%). Patients from the UMN site also had significantly fewer cNF and were more likely to have a higher Riccardi score.

The mean total Skindex scores were in the moderate range of severity among the UMN participants, while the RNS participants' mean was in the severe range (mean [SD] 22.4 [21.9] vs 38.8 [25.6], *p* = 0.004).²² There was a weak positive correlation between age and Skindex scores. The correlations are stronger, though still modest, at the UMN site and among the physical domain (table 2). When using data from both sites, the number of cNF was the most important clinical factor correlating with Skindex score in the regression model (relative importance of between 0.34 and 0.40, depending on the Skindex domain; figure and table 4). This is followed by sex, facial cNF, and site (figure and table 4). Riccardi score and age are not significantly correlated with Skindex scores in the models. These findings are consistent for all subdomains.

Table 4 Relative Importance of Clinical Factors Correlating With Skindex

	Total	Physical	Emotions	Functional
Both sites				
Number of NF	0.37	0.40	0.34	0.38
Sex	0.20	0.17	0.18	0.22
Facial NF	0.17	0.15	0.12	0.22
Site	0.15	0.14	0.18	0.09
Riccardi	0.07	0.09	0.13	0.05
Age	0.04	0.06	0.05	0.04
UMN				
Number of NF	0.44	0.38	0.45	0.46
Facial NF	0.31	0.14	0.31	0.34
Sex	0.13	0.26	0.10	0.10
Age	0.06	0.13	0.07	0.07
Riccardi	0.05	0.10	0.06	0.05
RNS				
Sex	0.35	0.11	0.41	0.39
Number of NF	0.22	0.24	0.20	0.22
Riccardi	0.24	0.38	0.26	0.26
Facial NF	0.13	0.24	0.06	0.11
Age	0.05	0.03	0.08	0.02

The relative importance measures of the various clinical factors for the multiple linear regression models for both sites, UMN separately, and RNS separately.

Whereas the average unadjusted difference in Skindex scores between sites was statistically significant, or near significant, adjusting for clinical factors reduced the size of these differences (table 3). After adjustment, the UMN site still had lower scores on average; however, these differences were no longer statistically significant, except in the emotion domain (*p* = 0.036).

Discussion

The findings of this study follow previous cohort studies that demonstrate an increase in skin-specific effect in patients with cNF as measured by Skindex, particularly in those with more visible disease.⁴⁻¹¹ Facial cNF and number of cNF yielded a higher effect on the Skindex scores, and this was true at each site. There were some site-specific differences in survey scores in our cohorts. However, when adjusting for sex, number of cNF, facial cNF, and age, the Skindex scores were more consistent.

The overall higher Skindex scores in the RNS cohort are likely to reflect the differing patient populations, with higher skin

symptomatology in a clinic specializing in cNF skin treatment vs a general NF clinic. QoL was significantly affected by sex, presence of facial cNF, and total number of cNF. Total number and facial involvement were the most important covariates in terms of overall effect across the Skindex domains, with the number of cNF showing a linear correlation and the greatest relative importance. Interestingly, Riccardi scores did not correlate well across domains, indicating that the Skindex tool should be used independently from Riccardi scores.

The location of neurofibromas is not assessed by existing patient-reported outcome questionnaires including Skindex. Our findings suggest this may be an important variable affecting QoL and should be considered in any future patient-reported outcome questionnaires.

Our findings that number of cNF, facial cNF, sex, and age can affect Skindex score suggest these measures will be important to consider in clinical trial design, as such factors could confound unstratified populations during site comparisons.

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Appendix (continued)

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Scott R. Plotkin, MD, PhD	Department of Neurology and Cancer Center, Massachusetts General Hospital, Boston	Study concept or design
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Christopher L. Moertel, MD	Department of Pediatrics, University of Minnesota, Minneapolis	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

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