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Pain, skin sensations symptoms, and cognitive functioning predictors of health-related quality of life in pediatric patients with Neurofibromatosis Type 1

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Abstract

Objectives The aim was to investigate pain, skin sensations symptoms and patient self-reported, and parent proxy-reported cognitive functioning as predictors of generic health-related quality of life (HRQOL) in pediatric patients with Neurofibromatosis Type 1 (NF1) from the perspectives of patients and parents.

Methods The Pain, Skin Itch Bother, Skin Sensations, and Cognitive Functioning Scales from the PedsQL™ Neurofibromatosis Type 1 Module and the PedsQL™ Generic Core Scales were completed in a multi-site national study by 323 patients and 335 parents. Patients were 5–25 years of age. Pain and skin symptoms and cognitive functioning were tested for bivariate and multivariate linear associations with generic HRQOL.

Results Pain, skin itch bother, skin sensations, and cognitive functioning were associated with decreased HRQOL in bivariate analyses ($P_s < 0.001$). In predictive analytics models, utilizing hierarchical multiple regression analyses controlling for demographic covariates, pain, skin itch bother, skin sensations, and cognitive functioning as a group accounted for 61 percent of the variance in patient-reported generic HRQOL ($P < 0.001$), reflecting a large effect size. For parent proxy-report, the predictor variables as a group accounted for 53% of the variance in generic HRQOL.

Conclusions Pain, skin symptoms, and patient self-reported and parent proxy-reported cognitive functioning are key predictors of generic HRQOL in pediatric patients with NF1. Delineating NF1-specific symptoms and cognitive functioning as high-priority predictors from the patient and parents perspective enhances a family-centered approach in clinical research, clinical trials, and clinical practice intended to improve the global generic HRQOL of pediatric patients with NF1.

Keywords Neurofibromatosis · Symptoms · Pain · Skin sensations · Cognitive functioning · Patient-reported outcomes · Health-related quality of life · PedsQL

The PedsQL™ is available at http://www.pedsql.org.

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Abbreviations

NF1	Neurofibromatosis Type 1
HRQOL	Health-related quality of life
PedsQL™	Pediatric Quality of Life Inventory™
PRO	Patient-reported outcome

Introduction

Neurofibromatosis Type 1 (NF1) is the most common autosomal dominant disorder of the nervous system. NF1 can impact the central and peripheral nervous system, manifesting malignant peripheral nerve sheath tumors, central nervous system gliomas, cognitive impairment, and plexiform neurofibromas [1, 2]. Past research has shown that NF1 has a deleterious effect on generic health-related quality of life

(HRQOL) [3]. However, the development of NF1-specific HRQOL instruments has been underinvestigated [4].

Recently, we described the development of the PedsQL™ Neurofibromatosis Type 1 Module utilizing cognitive interviews with children, adolescents, and young adults with NF1 and their parents [5, 6]. Throughout the individual interviews, pain, skin sensations, and patient self-reported and parent proxy-reported cognitive functioning emerged as salient symptoms of heightened concern for both patients and their parents. During the subsequent field testing of the PedsQL™ Neurofibromatosis Type 1 Module [7], these symptoms were demonstrated to be particularly problematic as reported by patients and their parents. In our field test study analyses, we demonstrated feasibility (low percentage of missing values), acceptable range of measurements, internal consistency reliability of the scales, determined the agreement between patient self-report and parent proxy-report, and demonstrated construct validity of the scales through factor analysis [7]. Nonetheless, to our knowledge there has been no published research that has investigated pain and skin sensation symptoms and patient self-reported and parent proxy-reported cognitive functioning as predictor variables of global general HRQOL in children, adolescent, and young adults with NF1.

To address this highly significant empirical gap in the pediatric NF1 research literature, the specific aim of the current study was to test predictive analytics conceptual models of pain, skin sensations symptoms, and patient self-reported and parent proxy-reported cognitive functioning as predictor variables of total general HRQOL in pediatric patients with NF1 utilizing the PedsQL™ Neurofibromatosis Type 1 Module database. We hypothesized that greater pain, skin sensations symptoms, and patient self-reported and parent proxy-reported cognitive functioning would be significant predictors of lower total generic HRQOL after controlling for demographic covariates in pediatric patients with NF1. We tested conceptual models of pain, skin sensations symptoms, and patient self-reported and parent proxy-reported cognitive functioning as predictor variables as a group as well as separate hierarchical multiple regression analyses to determine the unique variance accounted for by each of the individual symptom predictor variables, controlling for the demographic covariates.

Methods

Participants and settings

Pediatric patients with physician-diagnosed NF1 using the National Institutes of Health diagnostic criteria were recruited across the United States. Participants were recruited through the Children's Tumor Foundation (CTF) Neurofibromatosis (NF) registry, NF clinics at Indiana, Michigan, California, and Washington, D.C., and NF organizations including the Texas NF foundation, NF midwest, and NF network forums. A total of 343 families (323 pediatric patients and 335 parents) participated [7]. Patients were 5–25 years of age. Families completed the PedsQL™ measurement instruments either using paper mode of administration ($n = 204$, 59.5%) at home or Internet electronic model of administration at home ($n = 139$, 40.5%). The average age of the 169 boys (49.3%) and 174 girls (50.7%) was 12.38 years (SD = 5.89). With respect to race/ethnicity, the sample contained 256 (74.6%) White non-Hispanic, 23 (6.7%) Hispanic, 14 (4.1%) Black non-Hispanic, 3 (0.9%) Asian/Pacific Islander, 1 Native American (0.3%), other 30 (8.7%), and 16 (4.7%) missing. Parental informed consent and patient assent/consent (when age appropriate) were obtained. The research protocol was approved by the Institutional Review Board at Indiana University, Indianapolis (protocol # 1403632840).

Measures

PedsQL™ Neurofibromatosis Type 1 Module

The PedsQL™ Neurofibromatosis Type 1 Module items were developed through qualitative methods [5, 6]. The final instrument was derived from the field test study, demonstrating the reliability and validity of the PedsQL™ Neurofibromatosis Type 1 Module [7]. For the purposes of the present study, we utilized the following symptoms and cognitive functioning scales: Pain Scale (6 items, e.g., "I have pain so much that I need medicine"), Skin Itch Bother Scale (6 items, e.g., "My skin itches so much it is hard for me to sleep"), Skin Sensations Scale (3 items, e.g., "My skin feels like it is burning"), and Cognitive Functioning Scale (15 items, e.g., "It is hard for me to think quickly"). It should be noted that the Skin Itch Bother Scale and Skin Sensations Scale are the result of the factor analysis of the items in the original skin domain, in which the factor loadings indicated that three items were measuring a separate construct of skin sensations, while the remaining items were measuring a construct of skin itch bother [7]. Hence, the separation of these two skin-related symptoms scales.

The format, instructions, Likert response scale, and scoring method for the PedsQL™ Neurofibromatosis Type 1 Module scales are identical to the PedsQL™ 4.0 Generic Core Scales [8], with higher scores indicating better HRQOL and hence lower symptoms and problems. The scales are comprised of parallel patient self-report and parent proxy-report formats. The instructions ask how much of a problem each item has been during the past 7 days using the PedsQL™ 5-point Likert-type response scale (0 = never

a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). Items are reverse-scored and linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that lower scores demonstrate more NF1 symptoms and problems and hence lower NF1-specific HRQOL.

PedsQL™ 4.0 Generic Core Scales

The 23-item PedsQL™ 4.0 Generic Core Scales encompass: (1) physical functioning (8 items), (2) emotional functioning (5 items), (3) social functioning (5 items), and (4) school functioning (5 items) [8, 9]. To create the Total Scale Score, the mean is computed as the sum of the items divided by the number of items answered in the Physical, Emotional, Social, and School Functioning Scales. The Total Scale Score measures overall generic HRQOL [8]. Higher scores indicate better HRQOL.

PedsQL™ Family Information Form

Participants completed the PedsQL™ Family Information Form which contains demographic information including the child's age, gender, and race/ethnicity [8].

Statistical analysis

We conducted bivariate intercorrelations between the hypothesized NF1 predictor variables with global general HRQOL using Pearson product-moment correlation analyses. Effect sizes for bivariate intercorrelations are designated as small (0.10), medium (0.30), and large (0.50) [10]. Predictive analytics models employing hierarchical multiple regression analysis were conducted to statistically predict global general HRQOL by the PedsQL™ Neurofibromatosis Type 1 Module Pain, Skin Itch Bother, Skin Sensations, and Cognitive Functioning Scales as predictor variables, controlling for demographic covariates that were statistically significant at the univariate correlational analyses with the dependent variable [11].

The incremental variance accounted for by the predictor variables was tested through hierarchical multiple regression analyses [11]. Demographic control variables were entered in Step 1 as statistical covariates. The NF1 scale score was entered in Step 2 in separate hierarchical multiple regression models for patient self-report and parent proxy-report. The hierarchical multiple regression analyses controlled for demographic covariates that were correlated at the bivariate level with global general HRQOL, while demonstrating the incremental variance accounted for (R^2 change) by the NF1 predictor variables in Step 2. Multiple regression effect sizes (R^2) are designated as small (0.02), medium (0.13), and large (0.26) [10]. Statistical analyses were conducted using IBM SPSS Version 25 (Armonk, New York).

Results

PedsQL™ Neurofibromatosis Symptoms Scales, Cognitive Functioning Scale, and Generic Core scores means and standard deviations

Table 1 contains the means and standard deviations of the PedsQL™ Neurofibromatosis Scales scores and the Generic Core Total Scale Score for patient self-report and parent proxy-report. Cronbach's coefficient alpha was utilized to determine internal consistency reliability of the scales [12].

Table 1 PedsQL™ Neurofibromatosis Pain, Skin Symptoms, and Cognitive Functioning Scales and Generic Core Total Scale Scores Bivariate Correlations in Pediatric Patients with Neurofibromatosis Type 1

Neurofibromatosis Scales Scores and Generic Core Total Scale Score	Items	Patient self-report				Parent proxy-report			
		α	Mean	SD	r	α	Mean	SD	r
Pain	6	0.88	66.37	26.32	0.63*	0.91	66.81	26.14	0.59*
Skin itch bother	6	0.83	76.54	21.72	0.55*	0.89	74.89	23.14	0.47*
Skin sensations	3	0.82	83.49	22.57	0.51*	0.90	83.78	22.83	0.43*
Cognitive functioning	15	0.96	57.82	27.49	0.68*	0.97	51.20	27.56	0.60*
Generic Core Total Score	23	0.92	65.47	20.68	–	0.94	63.47	21.02	–

SD standard deviation, α Cronbach's alpha internal consistency reliability, r Pearson product-moment correlation coefficient

Bivariate correlations between the Neurofibromatosis Scales Scores with the Generic Core Scales Total Score

Effect sizes for Pearson r designated as small (0.10), medium (0.30), and large (0.50)

Lower scores demonstrate more (worse) symptoms and hence lower (worse) neurofibromatosis-specific HRQOL. Scale range = 0–100. Mean scores computed as the sum of the items divided by the number of items answered

*$P < 0.001$

Bivariate correlations between PedsQL™ Neurofibromatosis Symptoms Scales and Cognitive Functioning Scale with Generic HRQOL

Table 1 demonstrates the bivariate correlations between the PedsQL™ Neurofibromatosis Scales scores with the Generic Core Total Scale Score, demonstrating mostly large effect sizes.

Hierarchical multiple regression analyses predicting generic HRQOL

Prior to conducting the hierarchical multiple regression analyses, univariate analyses were conducted with age, gender, and race/ethnicity with the Generic Core Total Scale Score to determine which demographic covariates to include in the multivariate analyses as control variables. Age was significantly correlated with the Generic Core Total Scale Score for patient self-report ($r = -0.13$, $P < 0.05$) and parent proxy-report ($r = -0.13$, $P < 0.05$). Females demonstrated a lower Generic Core Total Scale Score than males for patient self-report (62.65 vs. 68.28, respectively, $t[318] = 2.45$, $P < 0.05$), but not parent proxy-report (62.98 vs. 63.96, respectively, $t[333] = 0.43$, $P > 0.05$). Race/ethnicity was not associated with the Generic Core Total Scale Scores for either patient self-report (F (3, 302) = 0.48, $P > 0.05$) or parent proxy-report (F (3, 320) = 0.85, $P > 0.05$). To be consistent across the patient and parent predictive conceptual models, age and gender were included as demographic covariates in all the multivariate analyses as control variables.

Table 2 presents the hierarchical multiple regression analyses predicting generic HRQOL for patient self-report and parent proxy-report. After controlling for the demographic covariates in Step 1, the PedsQL™ Neurofibromatosis Symptoms Scales and Cognitive Functioning Scale as a group in Step 2 significantly accounted for 61 percent of the variability in patient-reported generic HRQOL and 53 percent of the variability in parent proxy-reported generic HRQOL, representing large effect sizes.

We also conducted separate hierarchical multiple regression analyses to determine the unique variance accounted for by each of the individual symptom predictor variables, controlling for the demographic covariates. Table 3 contains the hierarchical multiple regression analyses predicting generic HRQOL separately for the PedsQL™ Pain Scale, Skin Itch Bother Scale, Skin Sensations Scale, and Cognitive Functioning Scale after for controlling for the demographic covariates. Patient self-reported and parent proxy-reported cognitive functioning and pain demonstrated the largest percent of the variability accounted for in generic HRQOL, followed by skin itch bother and skin sensations (all $P_s < 0.001$), demonstrating mostly large effect sizes.

Table 2 Hierarchical multiple regression analyses predicting Generic Core Total Scale Scores by the PedsQL™ neurofibromatosis predictor variables as a group controlling for demographic covariates

Predictor variables	Patient self-report	Parent proxy-report
Step 1. Demographic covariates		
Age (β)	−0.11*	−0.13*
Gender (β)	−0.11*	0.00
R^2	0.03**	0.02
Step 2. Neurofibromatosis predictor variables		
Pain (β)	0.34***	0.39***
Skin itch bother (β)	0.17*	0.10
Skin sensations (β)	0.08	0.03
Cognitive functioning (β)	0.43***	0.43***
R^2 change	0.61***	0.53***
R^2 full model	0.64***	0.55***

β Standardized regression coefficients (beta weights)

R^2 = Percentage of variability in the criterion variable (HRQOL) explained by the step

R^2 effect sizes designated as small (0.02), medium (0.13), and large (0.26)

Gender coded: 1 = male, 2 = female

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

Table 3 Hierarchical Multiple Regression Analyses Predicting Generic Core Total Scale Score by the individual PedsQL™ neurofibromatosis predictor variables controlling for demographic covariates in Step 1 (not shown)

Predictor variables	Patient self-report	Parent proxy-report
Step 2. Pain (β)	0.67***	0.62***
R^2 change	0.38***	0.34***
R^2 full model	0.41***	0.36***
Step 2. Skin itch bother (β)	0.58***	0.48***
R^2 change	0.33***	0.23***
R^2 full model	0.36***	0.24***
Step 2. Skin sensations (β)	0.49***	0.42***
R^2 change	0.24***	0.17***
R^2 full model	0.27***	0.18***
Step 2. Cognitive functioning (β)	0.67***	0.60***
R^2 change	0.44***	0.36***
R^2 full model	0.47***	0.37***

Gender coded: 1 = male, 2 = female

R^2 effect sizes designated as small (0.02), medium (0.13), and large (0.26)

β Standardized regression coefficients (beta weights)

R^2 = Percentage of variability in the criterion variable (HRQOL) explained by the step

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

Discussion

The findings support neurofibromatosis symptoms and patient self-reported and parent proxy-reported cognitive functioning collectively and individually as predictors of generic HRQOL, with large effect sizes. These findings represent an important and unique contribution to the NF1 empirical literature in that predictive analytics conceptual models utilized neurofibromatosis-specific symptoms and cognitive functioning in pediatric patients with NF1 from both the patient and parent perspectives. The study is further unique in testing separate predictive analytic conceptual models utilizing the PedsQL™ Neurofibromatosis Type 1 Module Pain Scale, Skin Itch Bother Scale, Skin Sensations Scale, and Cognitive Functioning Scale, in which was demonstrated the relative contribution of each latent construct in predicting generic HRQOL from the patient and parent perspective.

The findings that pain was an important symptom predictor of generic HRQOL are consistent with the empirical literature on the prevalence of pain in patients with NF1, including peripheral neuropathic pain and headaches [13–15]. Skin sensations have also been reported as common symptoms in NF1, with a relatively high prevalence of pruritus reported [16, 17]. Finally, moderate to severe impairment in cognitive functioning of patients with NF1 has also been demonstrated [18], with estimated rates of cognitive functioning problems as high as 80% of patients [19, 20], including executive functioning and attention deficits [21].

Although not an objective of the present study, generic HRQOL was reported as significantly impaired in this sample, consistent with the NF1 literature [3]. Based on previous PedsQL™ 4.0 Generic Core Scales findings, the Total Scale Score of 65.47 for patient self-report is almost 20 points lower than published data for healthy children and adolescents (83.84), while the parent proxy-report score of 63.47 is similarly lower than healthy children and adolescents (82.70) [22]. The scores for the present study are comparable to other severe chronic health conditions such as newly diagnosed pediatric cancer patients receiving chemotherapy and radiation therapy, in which the PedsQL Total Scale Scores are 68.92 and 66.95 for patient self-report and parent proxy-report, respectively [22]. It should be noted that these comparison scores are not matched for age and gender, but nevertheless provide a relative benchmark on the overall significantly impaired generic HRQOL of pediatric patients with NF1 in this sample.

The present study has several strengths, including the inclusive age range of ages 5–25 years, the large sample size for this rare disease, the nationwide recruitment, and the testing of a unique predictive analytics model with pain, skin sensations symptoms, and patient self-reported and parent proxy-reported cognitive functioning as NF1-specific predictors of global general HRQOL. Including both patient self-report and parent proxy-report further increases the unique contribution of the findings. Limitations include the absence of information in the database regarding the characteristics of any families who declined participation, and the lack of data on diagnostic categories such as ADD/ADHD and specific clinical subgroups such as patients with plexiform neurofibromas [23]. Although participants completed the PedsQL™ using either paper or Internet electronic modes of administration, previous PedsQL™ research has demonstrated the measurement equivalence of these two modes of administration [24].

Further studies administering the PedsQL™ Neurofibromatosis Type 1 Module may help develop a greater appreciation of the extensive range of neurofibromatosis-specific symptoms and patient self-reported and parent proxy-reported cognitive functioning problems that affect the overall HRQOL of these patients. As new pharmaceutical agents are developed for patients with NF1 [2, 25], these PedsQL™ neurofibromatosis-specific scales may help delineate patient symptoms and patient self-reported and parent proxy-reported cognitive functioning profiles as more precise targets for symptom-specific treatment interventions to increase global general HRQOL.

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Compliance with ethical standards

Conflict of interest Dr. Varni holds the copyright and the trademark for the PedsQL™ and receives financial compensation from the Mapi Research Trust, which is a non-profit research institute that charges distribution fees to for-profit companies that use the Pediatric Quality of Life Inventory™. The other authors report no competing interests related to this study.

Informed consent Parental informed consent and patient assent/consent (when age appropriate) were obtained from all participating families included in the study.

Research involving human subjects The research protocol for the field test study was approved by the Institutional Review Board at Indiana University, Indianapolis. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committees.

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