Impact of Neurofibromatosis Type 1 With Plexiform Neurofibromas on Patient-Reported Health-Related Quality of Life

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BACKGROUND

- Neurofibromatosis type 1 (NF1) is an incurable genetic condition that affects 1 in 3,000 newborns worldwide.[1,2] The severity of signs and symptoms associated with NF1 can be highly variable and may include skin, nerve, and skeletal manifestations[3]
- Approximately 25% to 50% of patients with NF1 develop plexiform neurofibroma (PN), which are benign nerve sheath tumors that grow along the length of nerves and involve multiple branches of a nerve[4,5]
- NF1-related PN can cause substantial morbidity, including pain, disfigurement, neurological deficit, difficulties with swallowing and breathing, potentially life-threatening hemorrhage, and the risk of malignant transformation[6]
- The significant symptom burden of NF1 + PN highlights the importance of measuring health-related quality of life (HRQOL) in clinical research and practice

OBJECTIVE

- To identify the patient-reported HRQOL of patients with NF1 and PN

METHODS

- A systematic literature review (SLR) was conducted in PubMed, Embase, and the Cochrane Library from January 1, 2009, to May 31, 2019, using search terms for impact on patient (all ages) HRQOL. The HRQOL SLR was part of a broader SLR to understand patient characteristics, treatment patterns, and health care resource use and costs associated with NF1 + PN

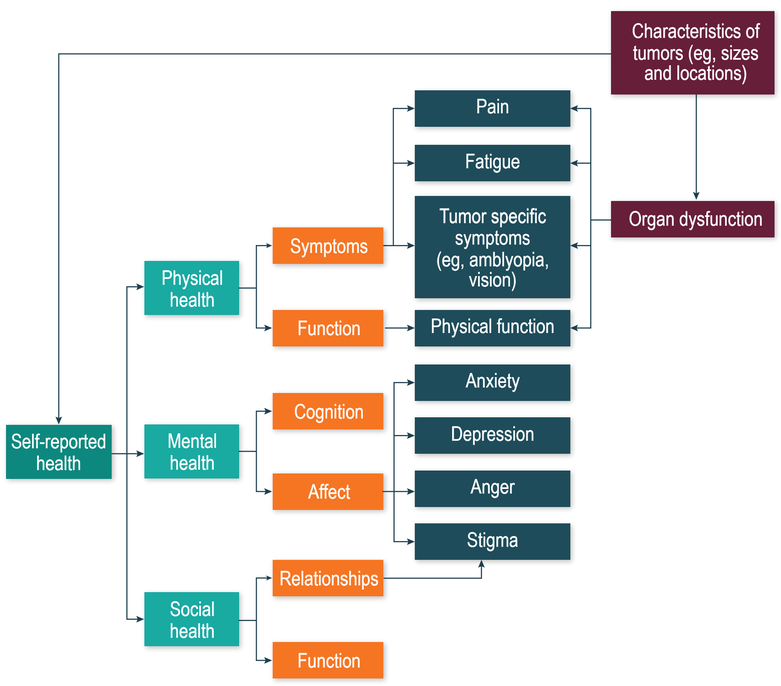
RESULTS

- Seven studies were identified that described the HRQOL of child, adolescent, and adult patients with NF1 + PN, including development of a conceptual model (n = 1), conduct of an HRQOL cross-sectional survey study (n = 2), conduct of a phase 2 longitudinal study measuring HRQOL (n = 1), and measurement of pain interference with HRQOL (n = 3). Most of the studies were conducted in the United States (n = 5), except for one study conducted in the United States and Germany[7] and one study conducted in France.[8] Most studies were conducted in children and adolescents (n = 5), except for one study conducted in children, adolescents, and adults[9] and one study conducted in adults only[13]

Conceptual Model for Measuring HRQOL in Patients With NF1 + PN

- A qualitative study was conducted to create a conceptual model that captures the experience of patients with NF1 + PN from the perspective of patients (n = 31, aged 5 years and older; mean age 23.9 [standard deviation (SD) 16.4]), parents (n = 17), and clinicians (n = 8). Results were the following[9]:
  - The most frequently reported concerns raised by patients across all age groups included pain, appearance/disfigurement, social activity/role participation, stigma, and anxiety
  - For parents, physical functioning was the primary concern, followed by pain, social activity/role participation, appearance/disfigurement, and social relationships
- **Figure 1** shows the conceptual model for measuring HRQOL in patients with NF1 + PN. The five domains that represented the most important symptoms/concerns were: pain, social functioning, physical function impact, stigma, and emotional distress[9]

Figure 1. Conceptual Model for Measuring HRQOL in Patients With NF1 + PN

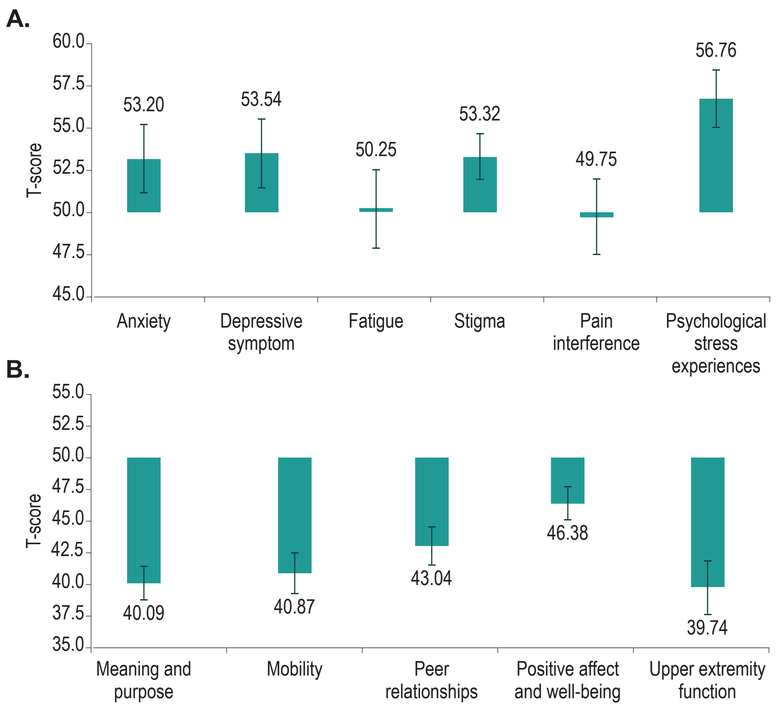


Source: Lai et al.[9]

HRQOL in Patients With NF1 + PN Compared With Normal Populations

- Although a pediatric, NF1-specific, patient-reported outcome (PRO) measure was recently developed (i.e., PedsQL Neurofibromatosis Type 1 Module for children, adolescents, and young adults) (Nutakki et al.[11] as cited in Lai et al.[12]), no published pediatric measure for NF1 + PN was identified in this SLR
- A study was conducted to assess the HRQOL of children with NF1 + PN using a battery of PRO measures selected based on the conceptual framework created in an earlier study by Lai et al[9,12]
- In total, 140 children with NF1 + PN aged 8-17 years completed the Patient-Reported Outcomes Measurement Information System (including the domains of anxiety, depressive symptoms, psychological stress experiences, fatigue, pain interference, meaning and purpose, positive affect, peer relationships, and physical function/mobility) and the 8-item stigma domain from the Quality of Life in Neurological Disorders measurement system online[12]
- **Figure 2A** and **2B** shows the child-reported HRQOL compared with the norming sample in which the normal mean is 50 and the SD is 10[12]
  - For all domains except fatigue and pain interference, respondents reported significantly worse scores than normal
  - Children with pain reported significantly worse symptoms and functioning on all domains
  - Boys reported significantly worse pain interference, stigma, meaning and purpose, mobility function, and upper extremity function than girls

Figure 2. Child-Reported HRQOL With NF1 + PN Compared With a Norming Sample



Note: mean = 50; SD = 10.
Notes: Error bars represent 95% confidence interval. (A) Measures with higher scores represent worse functioning = anxiety, depressive symptoms, fatigue, stigma, pain interference, and psychological stress experiences; (B) Measures with higher scores represent better functioning = meaning and purpose, mobility, peer relationships, positive affect and well-being, and upper-extremity function.
Source: Lai et al.[12]

- Using whole-body magnetic resonance imaging with the SF-36 and a visual analog scale for pain, the association between tumor burden and QOL in adults with NF1 (n = 142), NF2 (n = 53), or schwannomatosis (n = 50) was assessed using a convenience sample of patients seen at the NF clinics at Massachusetts General Hospital and University of Hamburg, Eppendorf, Germany. For patients with NF1, 60% had internal tumors, with a median tumor volume of 105.4 mL (range, 2.7-9,106.1)[7]
  - Patients with NF1 and tumor burden assessment had significantly lower scores on the physical functioning, physical role, general health, emotional role, and mental health subscales compared with the weighted United States population (P <0.05 for all subscales)
  - Log tumor volume was not found to be associated with QOL in the sample of patients with NF1 and tumor burden assessment, but age emerged as a strong predictor of QOL across multiple subdomains (increased age predicted decreased QOL)
  - Patients with NF1 and tumor burden assessment had significant deficits in the mental domains of the SF36

HRQOL of Patients With NF1 + PN Compared With Patients With NF1 Without PN

- In another cross-sectional study using two questionnaires (DISABKIDS and the Children's Dermatology Life Quality Index or CDLQI), HRQOL in patients with NF1 + PN (n = 5) was significantly more altered than in patients with NF1 without PNs (n = 68) as measured by the CDLQI for the following scores[8]:
  - Symptoms and feelings: 26.7 ± 11.3 vs. 7.1 ± 1.9; P = 0.005
  - During school or holidays: 20.0% ± 13.3 vs. 2.5% ± 1.3; P = 0.007

Impact of PNs on Daily Functioning and QOL in Patients With NF1 + PN

- To understand the impact of PNs on daily functioning and QOL in adolescents and young adults with NF1 + PN, PROs collected prior to treatment in NF1 + PN clinical trials were evaluated[13]
- All patients aged older than 16 years with NF1 and symptomatic inoperable PNs who were enrolled in NF Clinical Trials Consortium PN treatment trials completed a background information form, the Numeric Rating Scale (NRS11), the Brief Pain Inventory (BPI) Pain Interference Scale, and the NF1 PedsQL Scale at baseline (n = 38; median age, 23 years; range, 16-39)[13]:
  - 42% took pain medication regularly, with 23% taking prescription medication
  - Only 32% were employed despite 68% having completed high school or some college
  - On the NRS11 (0-10 scale), mean overall tumor pain was 5.3 (+3.0) with 90% rating some level of tumor pain (21% mild, 29% moderate, and 40% severe)
  - On the BPI (0-10 scale), general pain interference in daily life was 3.0 (+2.9)
  - On the NF1 PedsQL, the mean Total Functioning Score (0-100 scale, higher score is better) was 68.1 (+19.6)
  - Baseline PN volume correlated with total functioning (P <0.05) but not with pain scores
  - Total functioning correlated with pain intensity and pain interference (each P <0.01)
  - The most-affected QOL domains were physical functioning, worry, pain/hurt, and fatigue; the least-affected domains were skin irritation, daily activities, and treatment anxiety
  - Self-selected tumor pain, overall tumor pain, pain interference, total functioning, physical functioning, communication, pain/hurt, movement balance, daily activities, fatigue, and treatment anxiety were significantly worse in those with more severe ratings of NF1 + PN symptoms (P <0.01)
  - Patients who were not regularly taking pain medication had significantly worse tumor pain, pain interference, total functioning, worry, pain/hurt, and paresthesias.
  - Tumor pain was significantly worse in women compared with men (each P <0.01)
  - There were no significant differences in any domain between employed and unemployed patients

Impact of Pain in Patients With NF1 + PN

- To assess the impact of pain in children and adolescents with NF1 + PN and its relationship to disease factors, social-emotional functioning, and QOL, caregivers of 59 children and adolescents with NF1 + PN (aged 6-18 years) and 41 of these children and adolescents (aged 10-18 years) completed questionnaires to assess social-emotional functioning and QOL, including an item on pain interference[10]
- The QOL study was part of the Natural History Study of Patients with NF1 longitudinal study[10]
- Caregivers and adolescents completed the Impact of Pediatric Illness (IPI) scale, which is a general scale that assesses the effects of pediatric chronic illness on the domains of adaptive, emotional, physical, and cognitive functioning. Pain interference was assessed by one item on the IPI scale[10]
- The Behavior Assessment System for Children 2nd Edition self-report scale and parent rating scale were used to assess social-emotional functioning[10]
  - Children aged 6 to 18 years had caregiver ratings that indicated pain was interfering with their daily activities to some degree
  - Caregiver ratings of their child's pain interference did not differ from patient self-reported ratings
  - When comparing disease severity groups, pain interference was significantly higher in children and adolescents who had moderate to severe NF1 disease compared with those who had mild disease by both proxy and self-report
  - In total, 90% were taking prescription pain medications or a combination of over-the-counter and prescription pain medications
  - Despite taking pain medication regularly, 93% of these adolescents and 100% of their caregivers rated pain as interfering with functioning to some degree
  - Based on the caregiver behavior ratings, more symptoms of anxiety and larger tumor volumes predicted greater pain interference, while greater pain interference, worse depressive symptoms, and more disease complications predicted poorer QOL
  - As rated by adolescents, more symptoms of anxiety predicted greater pain interference, while greater pain interference and social stress predicted poorer QOL

Impact of Treatment for PN-Related Morbidities on Patients With NF1 + PN

- One longitudinal study (SPRINT phase 2 study; n = 50) for selumetinib in children aged 2-18 years with NF1 + PN collected PROs to assess tumor pain intensity (NRS11), pain interference in daily life (Pain Interference Index), QOL (PedsQL), and global impression of changes[14]
  - At baseline, 70% of patients had tumor pain (31% mild, 24% moderate, and 15% severe)
  - From baseline to cycle 12, 74% of patients had clinically significant decreases of > 2 points in their physician-selected target tumor pain, of which 79% had a partial response
  - Parent total QOL scores and physical, emotional, and social (but not school) domain scores improved significantly (each P <0.01)
  - Child physical domain scores improved significantly (P <0.05)
  - Parent/child median cycle 12 global impression of change ratings both indicated "much improved" change in tumor pain and other tumor-related problems
  - In qualitative responses, the most frequent themes noted by parents and children were improved appearance, better function, and decreased pain

CONCLUSIONS

- A conceptual framework included five domains: pain, social functioning, physical function impact, stigma, and emotional distress
- Various HRQOL measures have been utilized in NF1 + PN studies, and all measures showed a negative impact of NF1 + PN across several domains
- Children with NF1 + PN reported worse HRQOL scores than population norms on most domains
- Children with NF1 + PN reporting pain also had significantly worse symptoms and functioning on most HRQOL domains compared with population norms. Pain interferes with daily functioning in most children and adolescents with NF1 + PN even when using pain medication
- NF1 + PN has a substantial impact on HRQOL, including physical, social, and emotional function and pain, highlighting the need for effective treatment options that can improve HRQOL

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