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Substantial Pain Burden in Frequency, Intensity, Interference and Chronicity among Children and Adults with Neurofibromatosis Type 1 Pain and NF1

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Abstract

Tumor growths, migraine headaches, and other health-related complications reported in patients with neurofibromatosis type 1 (NF1) are often associated with pain. Thus, this study sought to describe and quantify the pain experience in children and young adults with NF1.

Surveys were administered to 49 participants (28 children and 21 adults), ages 8 through 40 years. The survey included the Numeric Rating Scale 11 (NRS11) to assess pain intensity and the Patient Reported Outcomes Measurement Information System (PROMIS) to assess pain interference. A supplemental survey was created to measure pain frequency, chronicity, quality, and location.

Results suggest pain is not only present in 55% of the cohort, but that it can begin at early ages. Pain was chronic in 35% of participants, with 41% reporting the use of medication to manage pain symptoms. Common sources of pain included migraine headaches and NF-related tumors. Pain was described as having neuropathic features (i.e. burning, tingling, numbness, or itching), and was localized to the head, back, and extremities. Further, subsets of participants reported moderate-to-severe pain intensity, high frequency of pain, and interference of pain in daily activities. Continued investigation of the pain experience in a multisystem disorder, such as NF1, remains essential to providing guidance in the setting of complex pain management.

Keywords

Neurofibromatosis; NF1; pain; neuropathic pain; interference

INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant, neurologic genetic condition, with an estimated incidence of approximately 1 in 3,000 live births worldwide (Huson et al., 1989). NF1 is one of the RASopathy spectrum disorders and is caused by sporadic or hereditary germline mutations in the *NF1* gene encoding neurofibromin, a ubiquitous protein

highly expressed throughout the nervous system and multiple other tissue types (Nordlund et al., 1993).

There are many potential sources of pain in patients with neurofibromatosis. Plexiform neurofibromas (PN) are benign peripheral nerve sheath tumors that grow along nerves, can occur both internally and externally, and may result in severe and chronic pain in some patients. A subset of PNs occurs in the paraspinal region and can be particularly problematic. As a result of increased tumor growth, PNs have the potential to cause major obstructions, which can be linked to increased rates of morbidity and mortality (Tonsgard, 2006). Moreover, PNs have been noted to have a negative impact on an individual's quality of life via debilitating disfigurement, compression of vital structures, and unrelenting pain (North, 1997). In addition to PNs, there are a number of other factors contributing to pain in NF1, including but not limited to migraine headaches, cutaneous or nodular neurofibromas, pruritus, orthopedic pain from scoliosis or bone dysplasia, neuropathic pain from increased pressure on the nerves, and pain related to malignancy (North, 1997, Creange et al., 1999, DiMario et al., 2000, Tonsgard, 2006, Wolters et al., 2015)

Although pain is a frequent symptom of NF1, the characterization of the pain experience has received relatively little attention in published NF1 literature. Thus, NF1 and pain management specialists have begun to appreciate the importance of obtaining a full clinical picture to aid in identifying, understanding, and treating the pain experience in the NF1 population. The aim of this study was to describe and quantify the pain experience in children and adults with NF1. The results of our study may aid in the clinical evaluation of individuals with NF1 particularly when considering management and treatment strategies for pain.

MATERIAL AND METHODS

Recruitment:

Upon obtaining approval from the Cincinnati Children's Hospital Medical Center (CCHMC) Institutional Review Board, we conducted a cross-sectional study to characterize the pain experience in children and young adults with NF1. Participants surveyed included children (ages 8–17 years) and young adults (ages 18–40 years) with a confirmed diagnosis of NF1 based on molecular analysis or the National Institutes of Health (NIH) clinical criteria, who attended the Neurofibromatosis (NF) clinic at CCHMC, CCHMC general genetics clinics, the adult NF clinic at the University of Cincinnati Medical Center, and/or the annual NF Family Symposium held at CCHMC.

Study Procedure:

The individual pain experience was documented through a series of validated pain questionnaires, as well as a newly developed pain survey related to self-reported pain interference, intensity, chronicity, frequency, pain quality, and pain location. Paper-based surveys were administered to all child and adult participants, in-person, at the above-mentioned recruitment sites. A study staff member was available for participants who required assistance with completing the survey. Alternatively, some child participants

completed the surveys with the assistance of a present parent or guardian. If study participants opted to complete the survey, informed consent was implied. To note, omitted responses to any of the survey questions did not disqualify participants from inclusion in the study.

Validated questionnaires used in the survey included the Numeric Rating Scale 11 (NRS11) as a measure of pain intensity, and the Patient Reported Outcomes Measurement Information System (PROMIS) Short Form Pain Interference 8-item survey v1.0 for adults and the PROMIS Pediatric Short Form Pain Interference 8-item survey v1.0 for children. The NRS11 is designed on a 0–10 point scale (McCaffery et al., 1989) and is recognized as a standardized tool to measure worst, least, and current pain intensity in individuals 8 years and older (Pagé et al., 2012). In this study, the NRS11 was used to assess current pain and worst pain in the past 24 hours. The PROMIS pain inference assessment is an 8-question Likert scale based survey, which measured individual perceptions regarding pain interference within the past 7 days. Each item on the questionnaire has five response options, ranging in value from one to five for adults and zero to four for children. Raw scores were then summed and converted to a T-score with a mean of 50 and a standard deviation (SD) of 10, where the higher T-scores indicate worse pain interference. The PROMIS pain interference assessment tool was selected as it has been validated in youth and adults to measure perceived pain interference on daily life activities over time (Dampier et al., 2016). PROMIS measures are standardized to the United States general population and, therefore, provide reliable information to compare patient-reported outcomes from individuals with chronic disease to a group of non-diseased controls (Liu et al., 2010).

Additionally, a supplemental survey was created to collect general demographic information as well as to gather information regarding self-reported pain source, frequency, chronicity, quality, and location. The demographic section of the supplemental survey captured information such as sex, age, age at NF1 diagnosis, race, ethnicity, marital status (for adults), and highest level of education. To collect information regarding co-morbidities, we asked participants to indicate whether a doctor or other healthcare professional had ever diagnosed them with depression, anxiety, or a learning disability. Additional disease complications were collected through a yes/no question asking if participants regularly experienced pain. If the answer was yes, participants were then asked to self-report what they attribute those sources of pain to be. Participants could select all that apply from a 6-item list comprised of NF1 tumors, migraine headaches, non-migraine headaches, scoliosis, other, or unknown sources of pain. We collected pain frequency information by asking participants how often they felt pain (of any type) in an average seven-day week. For the purposes of our study, pain frequency was defined as “low frequency” (i.e. pain occurring less than 3 days per week) and “high frequency” (i.e. pain occurring 3 or more days per week). Chronic pain has been described as “persistent or recurrent pain lasting longer than three months” by the International Association for the Study of Pain Task Force (Treede et al., 2015). Pain chronicity was documented based on a yes/no question regarding the presence of pain persisting for 3 or more consecutive months, specifically within the past year. Pain quality was ascertained by allowing participants to choose physical descriptors of their pain such as itching, shooting, stabbing, or pinching types of pain. Pain location was assessed in terms of the self-reported anatomical location of the pain site on a body diagram. Lastly, the survey

asked if participants took prescription and/or over-the-counter medication to manage pain symptoms.

As this was a newly created supplemental survey, it was pre-tested on five adult individuals, without NF1, to provide an estimate of time taken to complete the survey, readability, clarity of questions, and overall face validity.

Data collected from the surveys was de-identified, manually entered, and securely stored in the HIPAA compliant REDCap database.

Statistical Analysis:

As our primary objective was to describe the pain experience, the analyses for this study were conducted using descriptive statistics. For dichotomous variables, frequencies were used. For continuous data, medians and interquartile ranges (IQR) were reported, as the data was not normally distributed. In addition, we sought to determine if the pain experience differed in children and adults. To test for these differences, we used 2×2 contingency tables and Chi² goodness of fit tests for dichotomous outcomes and Wilcoxon rank sums for continuous pain scores.

RESULTS

Sample characteristics:

Forty-nine participants (28 children and 21 adults) with NF1 completed our pain survey between August 2016 and December 2016. Demographic characteristics for children and young adults are summarized in Table I. The sample consisted of participants between the age of 8 and 40 years. The median age of adults was 31 years old, and the median age of children was 12 years old. Over half of the participants were female (57%), and the majority (92%) reported Caucasian ancestry.

Pain frequency and chronicity:

On the supplemental survey, 27 (55%) of the 49 participants reported regularly experiencing pain (46% of children, 67% of adults) (Table II). Furthermore, 35% of all participants (25% of children and 48% of adults) reported their pain to be chronic in nature (defined as pain lasting ≥ 3 months in the past year). Of the total group, 41% of participants (29% of children and 57% of adults) reported a high pain frequency (defined as pain present on 3 or more days per week).

Pain intensity:

Results from the NRS11 (Table II), show that 47% of all participants reported NRS11 scores consistent with no current pain on the day of survey (NRS11 current pain = 0); 54% of children, 38% of adults), while 39% of participants (46% of children, 29% of adults) reported no pain over the past 24 hours (NRS11 worst pain = 0). In contrast, 22% of participants in the total sample reported moderate to severe current pain (NRS11 ≥ 4 (McCaffery et al., 1989)); 11% of children, 38% of adults) while 45% of participants (32%

of children and 62% of adults) reported their worst pain over the past 24 hours as moderate to severe.

Pain interference:

PROMIS pain interference levels reported in the total group did not appear to indicate significant pain interference associated with NF1 (children n=28, median= 48.7 [34–59 IQR]; adults n=21, median= 56.9 [44.2–64.4 IQR]) (Table II). However, PROMIS pain interference levels were slightly elevated above the reference (T-score of 50) among those children and adults who specifically reported regularly experiencing pain (Table II) with similar results in those who reported chronic pain (data not shown in Table II). Further, 46.2% of children (n=6/13) and 50% of adults (n=7/14) reporting regularly experiencing pain had PROMIS T-scores above 60, which is one standard deviation above the reference T-score (Table II).

Pain characteristics:

Overall, patients with NF1 commonly reported pain occurring in the head, back, and extremities (Figure 1). Importantly 35% of the total cohort (25% of children, 48% of adults) and 58% of those reporting pain, selected descriptors typically attributed to neuropathic pain (i.e. including burning, tingling, numbness, and itching) to describe their pain qualities. Specifically, frequent itching, which shares a common neural pathway with pain (Twycross et al., 2003) was reported in 36% of participants (29% of children and 48% of adults) and in 41% of the participants that regularly experienced pain.

Headache pain:

Relatively high frequencies of headache related pain was reported in 41% of the overall study population (32% of children and 53% of adults, Figure 2), with most of these participants reporting migraine-headache related pain. Specifically, 31% of participants identified migraine-headaches as a significant source of pain (38% of children and 25% of adults, Figure 3).

Non-headache pain:

Non-headache pain was reported in 45% of the total sample (32% of children and 62% of adults, Figure 2). Other common sources of pain included tumor-related pain (usually plexiform neurofibromas), which was reported in 27% of all study participants, while scoliosis-related pain was reported in 14% (Figure 3).

Pain Management:

A total of 20 participants (41%; n=12 children and 8 adults) reported taking medication for pain, either over the counter (acetaminophen, ibuprofen) or prescription grade (Gabapentin, codeine). The most commonly reported prescription medication taken to manage pain symptoms was Gabapentin.

Co-morbidities:

A diagnosis of anxiety and/or depression was reported in 43% of adults and 32% of children. Participants with chronic pain were more likely than those without chronic pain to report having depression (47% vs. 9%, $p=0.005$). While there was also an increase in reported diagnoses of anxiety among individuals with chronic pain versus those without chronic pain (47% vs. 25%), this comparison did not reach statistical significance.

Significant differences in the pain experience among children and adults:

The frequency of pain in an average 7-day week differed between children and adults (Table II). When looking at the total sample, approximately 57% of adults reported high pain frequency (i.e. pain ≥ 3 days per week), compared to 29% of children ($p=0.04$). Moreover, there was a significant difference between children and adults with regard to multiple sources of pain. Of those patients reporting pain, 93% of adults ($n=13/14$) reported multiple sources of pain, including combinations such as migraine headaches and NF1-related tumors, in contrast to 38% of children ($n=5/13$) ($p=0.004$).

DISCUSSION

While many clinicians report their patients with NF1 experience considerable pain, there is little documentation specifically describing the pain experience. Our study sought to fill this gap in the literature in order to help describe pain characteristics in children and young adults with NF1 and to further define the impact of the pain experience. We found that both children and adults experience substantial pain burden, but their experiences differ. Specifically, regardless of age, approximately half of patients with NF1 experience pain often throughout the week and a subset has pain of moderate to severe intensity. Through patient reported outcomes, approximately half of individuals experiencing regular pain indicated that their pain is substantial enough to interfere with daily living. The most common sources of pain reported by participants were NF tumors as well as migraine and non-migraine headaches, with more adults reporting multiple sources of pain than children. Moreover, we found that pain among children and adults often has neuropathic-like features, is often chronic in nature, and may be accompanied by comorbidities such as anxiety and depression. This work provides an essential first step in better characterizing the pain experience in patients with NF1.

Within our cohort of children and young adults with NF1, we found that 55% of participants regularly experience pain of any type, with 41% reporting headache pain and 45% with non-headache related pain. Interestingly, this suggests a greater prevalence of pain among those with NF1 than previously reported by Riccardi (1992) and Creange et al (1999). It should be noted that these prior studies did not assess pain frequency in their NF population by use of specific pain questionnaires or tools, and therefore, the higher pain frequency found within our cohort is expected to be closer to a true estimate. Our findings regarding headache-related pain are somewhat higher than previous reports, which noted the presence of migraine and non-migraine headaches in 18–30% of patients with NF1 (Creange et al., 1999, Clementi et al., 1996). This observation is further corroborated in a publication by DiMario and Langshur (2000), which concluded that patients with NF1 are at a significantly

greater risk for headache-related pain when compared to the general population. Although inconsistencies identified in the approximate rates of pain in patients with NF1 are to be taken with caution, our findings emphasize the importance of recognizing pain as a significant burden of NF1.

We also found that pain was reported to occur at a high frequency and intensity in a subset of patients, resulting in substantial interference with overall daily life, despite a considerable proportion of individuals taking medication to manage pain. Our findings regarding pain interference are consistent with Wolters et al., (2015), who observed that in a cohort of children with NF1 and plexiform neurofibromas (PNs), pain interfering with daily functioning was documented in over 60% of participants. Although the study performed by Wolters et al. was executed with a selective population of children with large PNs, the results of this investigation support our findings regarding considerable pain interference and highlight the impact of pain on patients with NF1. Additionally, Wolters and colleagues (2015) identified that 33% of children with NF1 take daily pain medications, including over-the-counter pain relievers and/or prescription medications. Despite the daily administration of pharmaceuticals for pain management, medication did not appear to sufficiently control pain in most. This discovery is similar to our findings and further emphasizes the clinical necessity to address unmet needs of patients coping with pain. Therefore, it is crucial to keep in mind current treatment strategies, efficacy, and their therapeutic relationship on relative levels of pain when evaluating this population of patients.

Further, we noted that patients experiencing pain were more likely to report a diagnosis of anxiety and/or depression. This observation is consistent with previous research, which demonstrates that living with this chronic genetic condition impacts psychosocial wellness (Johnson et al., 1999, Creange et al., 1999, Noll et al., 2007). Neurobiological researchers suggest pain and emotion are interconnected in such a way that emotional distress may negatively influence an individual's perception of pain severity and intensity (Gatchel et al., 2007). Ultimately, continued investigation involving social-emotional functioning in an NF1 population would help to establish adequate treatment recommendations and therapies for patients with pain and comorbid anxiety or depression (Page et al., 2006, Garwood et al., 2012).

Age-related differences among patients with NF1 were observed in the frequency and source of pain. Specifically, adults were more likely to report pain, and experienced more headache and non-headache related pain when compared to children. However, children also frequently reported pain, with a subset experiencing substantial intensity and interference. Evidence reported by Chrusciel and colleagues (2009) substantiate our findings, which indicate that unlike a population of healthy children, pain can present at a young age and is in fact common in children with NF1. However, it is important to note the comparisons of children and adults must be interpreted with caution given the small sample size of our cohort.

Limitations

Continued investigation into the pain experience in patients with NF1 is needed to address the limitations of our study. First, the newly developed survey was pre-tested on five adult,

non-NF individuals, during the pilot phase. Given this survey was created for both children and adults with NF1, it is possible that we did not accurately capture the pain experience in some of our participants. Specifically, our younger study participants or adults with learning disabilities may have faced challenges with the terminology used in the survey. Study staff was available for assistance, but it is possible that not all participants voiced the need for support. Additionally, parents who assisted their children may have influenced their responses. Second, when assessing pain frequency in the newly created survey, we asked participants to report how often they felt pain (of any type) in an average 7-day week. This leaves room for participants to report the worst pain in the worst week, which may artificially inflate the frequency of pain reported in this subset of patients with NF1. Lastly, a majority of our study participants were female and of Caucasian ancestry, which limits the generalizability of our findings. Given the small sample size and subjective nature of our survey, the results from our study are to be interpreted with caution. Although our study made some direct comparisons between the pain experience in children and young adults with NF1, additional comparisons, such as looking at how the pain experience might differ between male and female patients with NF1, are certainly warranted.

Conclusions

Importantly, these results have provided valuable information with regards to the pain experience among patients with NF1. Most notably, our preliminary study has identified that regardless of age, pain is present in patients with NF1, it can begin early (i.e. as young as 8 years old), it is commonly described as neuropathic-like and chronic in nature, and the overall pain experience results in substantially high levels of interference and intensity among these individuals. It will prove beneficial for future studies to consider the longitudinal implications of pain in individuals with NF1, such that specialists and providers may tailor information and guidance regarding chronic pain management as well as psychosocial considerations for quality of life. Studies that aim to describe the pain experience over time may also contribute to the on-going efforts of clinical trials, where pain outcomes are becoming increasingly important in monitoring the efficacy of novel targeted therapies for NF1.

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Figure 1.
Location of pain reported in children and adults with NF1 (N=49)

Figure 2.
Headache versus non-headache related pain reported in children and adults with NF1
(N=49)

Figure 3.
Reported source of pain in children and adults with NFI (N=49)

Table I.

Demographic Characteristics of Total Study Population

Characteristic	Total Sample (N = 49)	Children (n = 28)	Adults (n = 21)
Age			
Median age in years [IQR]	16[11.5–29.5]	12[9.25–14]	31[25.5–33.5]
Sex			
	n (%)	n	n
Female	28 (57.1%)	12	16
Male	21 (42.9%)	16	5
Race			
Caucasian	45 (91.8%)	26	19
African American	3 (6.1%)	1	2
Mixed	1 (2.1%)	1	0

IQR: Interquartile Range.

Table II.**Pain Burden in Intensity, Interference, and Frequency**

	Children (n = 28)	Adults (n = 21)	P-value
NRS11 Pain Intensity			
Current Pain Intensity (median (IQR))	0 (0–2)	3 (0–5.5)	0.08
None (NRS11 = 0)	15 (53.5%)	8 (38.1%)	
Mild (NRS11 1–3)	10 (35.7%)	5 (23.8%)	
Moderate (NRS11 4–6)	1 (3.6%)	7 (33.3%)	
Severe (NRS11 7–10)	2 (7.1%)	1 (4.8%)	
Worst Pain Intensity (median (IQR))	1 (0–5.5)	6 (0–7.5)	0.09
None (NRS11 = 0)	13 (46.4%)	6 (28.6%)	
Mild (NRS11 1–3)	6 (21.4%)	2 (9.5%)	
Moderate (NRS11 4–6)	3 (10.7%)	5 (23.8%)	
Severe (NRS11 7–10)	6 (21.4%)	8 (38.1%)	
PROMIS Pain interference[†] (median (IQR))			
	48.7 (34–59.0)	56.9 (44.2 – 64.4)	--
% Above T score 50 among those with pain	9 (69.2%)	13 (92.9%)	
% Above T score 60 among those with pain	6 (46.2%)	7 (50.0%)	
Self-Report			
Regular Experience Pain (% Yes)	13 (46.4%)	14 (66.7%)	0.15
Chronic Pain > 3 months (% Yes)	7 (25.0%)	10 (47.6%)	0.10
High frequency pain (% >3 days)	8 (28.6%)	12 (57.1%)	0.044

[†] Children and adults cannot be compared as PROMIS pain interference scoring differs between the two age groups.

IQR: Interquartile Range.