Health-related Quality of Life of Individuals With Neurofibromatosis Type 2

Health related quality of life of individuals with neurofibromatosis type 2: Results from the NF2 Natural History Study

Running head: Quality of life in NF2

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ABSTRACT

Objective: To explore health-related quality of life (HRQoL) reported by individuals with neurofibromatosis type 2 (NF2) and to assess for correlations between HRQoL and objective measures of disease manifestations.

Study Design: Prospective observational study.

Setting: Seven international NF2 centers

Subjects: 81 individuals with NF2, 73 adults (>18 years) and 8 children/adolescents (10-17 years)

Outcome Measures: Quality of life was measured by SF-36 norm-based scores. Objective clinical measures were hearing (categorized by word-recognition scores), facial function (categorized by the House-Brackmann scale) and the volume of subjects' larger vestibular schwannoma (VS).

Results: At baseline, adults showed significant deficits in all but two subscales of the SF-36 compared to age- and gender- adjusted US population norms. In linear regression models including age, gender, inheritance status, hearing, facial weakness and VS volume, demographic and functional measures showed no relationship to any SF-36 subscale. Larger baseline VS volume was significantly related to reduced physical role performance, reduced mental health, and increased pain ($p<0.05$). In bivariate analysis, prior VS surgery was not significantly associated with baseline HRQoL; receipt of VS surgery or tumor growth during the observation period was not significantly associated with changes in HRQoL.

Conclusion: NF2 patients report reduced HRQoL in physical, social, and mental domains, but this was not significantly related to objective measures of hearing or facial functioning. Larger baseline VS volume negatively impacted patient-reported HRQOL whereas VS surgery or tumor

growth did not. Future studies should explore the relationship between tumor volume and HRQoL and psychosocial factors that may moderate this relationship.

INTRODUCTION

Neurofibromatosis type 2 (NF2) is a neurogenetic tumor suppressor syndrome, with an estimated birth incidence of 1:25,000.(1) NF2 is characterized by the development of bilateral vestibular schwannomas (VS), as well as schwannomas of other cranial nerves, meningiomas, and spinal ependymomas.(2) Over time, patients typically lose hearing, and may acquire other neurological deficits, such as facial weakness, balance difficulties, and gait instability due to non-vestibular schwannomas or complications of treatment. These medical complications may lead to difficulties coping and significant psychosocial distress, including decreased health-related quality of life (HRQoL).

While prior studies have documented an association between patient reported disease characteristics and HRQoL in patients with NF2, it is unclear whether HRQoL correlates with clinically observed disease manifestations in this population.(3-6) Thus far, demographic and clinical factors that include age, gender, total peripheral tumor volume, and presence of non-vestibular schwannomas and meningiomas have not been found to be associated with HRQoL (except in limited areas).(6;7) However, the relationship between VS volume and HRQoL has not been assessed in patients with NF2. And while patient reported impact of hearing difficulties and facial weakness has been correlated with reduced HRQoL in NF2,(3;6) no prior HRQoL studies have used objective clinical measures for hearing or facial function.

In order to further assess whether a relationship exists between objectively measured clinical findings and HRQoL in patients with NF2, we analyzed results from the NF2 Natural History Study (NF2NHS), the largest known international sample of NF2 patients with both prospective medical and HRQoL evaluation. Analyses of serial MRI and audiometry studies from this study have been reported in previous publications,(8-11) and here we report for the first

time Short Form-36 (SF-36) results. Specifically, we aimed to 1) assess patient-reported quality of life in a large cohort of international NF2 patients and 2) explore any associations between HRQoL, demographic characteristics, and objective clinical features.

MATERIALS AND METHODS

Study Cohort

All subjects who were enrolled in the NF2NHS between 1999-2001, were English-speaking, and received HRQoL assessments were included in the current analysis (see Supplemental Digital Content 1 for full list of centers and principal investigators). NF2NHS participants were aged 5 years or older, carried a diagnosis of NF2 according to National Institutes of Health criteria,(12) had at least 1 untreated vestibular schwannoma, and had been diagnosed with NF2 within the 5 years prior to enrollment. During this observational study, subjects received medical care as directed by their treating physicians; subjects treated with surgery after enrollment were not removed from the study.

Data Collection

Prospective data was collected annually and included audiometry, neurological function assessment, and HRQoL assessment. MRIs ordered as part of clinical care were recorded. Audiometry included determination of pure tone thresholds and word recognition scores.(13;14) Neurological function assessment included physician grading of facial function using the House-Brackmann scale.(15) Health-related QoL was measured by patient self-report using the SF-36 version 1.

The SF-36 is a 36-item questionnaire which assesses patient-reported HRQoL over the prior month. Scores are reported for 8 subscales: physical functioning, physical role, bodily pain, general health, vitality, mental health, social functioning, and emotional role. Score are

also reported for two summary scales (the physical component summary scale and mental component summary scale), which reflect a more general perception of HRQoL.(16) Norm-based scores were calculated for each respondent using the QualityMetric Health Outcomes™ Scoring Software 2.0.(17) This software transforms raw scores for each scale into a norm-based score with an expected mean of 50 and standard deviation of 10, using data from a representative sample of the 1998 non-institutionalized general US population. For all SF-36 subscales, higher scores reflect increased HRQoL (i.e. better physical functioning, less pain) and lower scores reflect decreased HRQoL.

Statistical Analyses

We report descriptive statistics for clinical and demographic factors for the study cohort. As the SF-36 was validated in the adult population, age and gender population means are only available for adults age 18 and up. For this reason, we used a one-sample t-test in to compare the mean SF-36 norm-based scores of adults with NF2 only to age and gender adjusted general population means. Given the lack of population norms for children age <18, norm-based scores of children with NF2 are presented descriptively, without statistical comparison.

We used multivariable linear regression to analyze the relationship between clinical and demographic factors with each HRQoL subscale at baseline. Multivariate models included age, gender, sporadic vs. familial inheritance, hearing status, facial function and vestibular schwannoma volume. Hearing status was categorized as no hearing loss (WRS ≥ 50% in both ears), unilateral hearing loss (WRS <50% in one ear only), and bilateral hearing loss (WRS <50% in both ears). A word recognition score of <50% was used as the cut-off for hearing loss to correspond with the American Academy of Otolaryngology-Head and Neck Surgery (AAO-

HNS) hearing classification system's Class D hearing, which constitutes "nonfunctional hearing". Facial function was dichotomized as no facial weakness (House-Brackmann score of 1 or 2) or facial weakness on one or both sides of the face (House-Brackmann score ≥3). A cut-off of 3 was chosen for facial weakness as this indicates moderate dysfunction with obvious weakness.(15)

VS volume was analyzed using the baseline volume of the subject's larger VS. Cumulative tumor volume (from both VS) was not used because the clinical impact of having one large tumor and one small tumor may be larger than that of two medium sized tumors, and use of a single VS volume allows us to retain the distinction between these two situations. Entry into the NF2NHS required only one untreated VS, and prior VS surgery in the contralateral ear may influence HRQoL. However, our sample size limited the number of independent variables that could be included in this multivariate model. For this reason, we performed a separate Wilcoxon rank-sum tests to compare baseline SF-36 scores of subjects who had and had not received VS surgery prior to survey administration. Age at diagnosis and duration since diagnosis were highly correlated with current age; for this reason, neither factor was included in our analyses.

To assess change in HRQoL over time, we used paired-sample T-tests to compare changes in each HRQoL subscale scores over 2 years. We also used Wilcoxon rank-sum test to investigate if receipt of VS surgery during the study or increase in volume ≥20% of the subjects' larger VS was associated with changes in HRQoL over time. These two factors were selected post-hoc after reviewing the findings of the baseline HRQoL model. Due to the limited sample size of the subcohort with longitudinal data and the desire to limit bias due to multiple testing, no other bivariate or multivariate models were assessed for change in HRQoL over time.

All statistical calculations were performed using SAS software (version 9.3, SAS Institute Inc, NC, USA). The NF2NHS was approved by the institutional review board (IRB) of each institution in the NF2 Natural History Consortium and by the central Department of Defense IRB. All patients provided written informed consent. Re-analysis of the study data was approved by the Partners Human Research Committee.

RESULTS

Study Cohort

A total of 141 subjects were enrolled in the NF2NHS, and 81 (57%) were eligible for analysis. Among 60 ineligible patients, 20 (14%) subjects were non-English speaking, 20 (14%) subjects had discontinued participation in the study before introduction of the HRQoL assessment in 2002 and 14 (10%) subjects did not complete their baseline SF-36 assessment.) 73 adults and 8 children with an overall median age of 31 years (range, 5 to 78 years) were included in the current study. 17 subjects (21%) had a known family history of NF2 and 51 subjects (63%) had undergone vestibular schwannoma surgery prior to their baseline SF-36 assessment. Baseline clinical characteristics of the subjects included in the current study are shown in Table 1.

Baseline HRQoL of adults with NF2

Adult subjects (age >18 years) scored significantly lower on 6 of 8 domain-specific subscales when compared to weighted US population means ($p<0.05$ for all), specifically in physical function, physical role, general health, emotional role, mental health and social functioning (Table 2). In addition, adult subjects had significantly lower physical and mental summary scores when compared to the general population ($p<0.05$). General health was the most

affected domain with an average score of 43.9, a moderate-sized difference of 6.7 points compared to matched general population scores. In multivariate models examining the relationship of clinical and demographic factors to SF-36 subscale scores in adults, there were no significant relationships between age, gender, inheritance status (familial vs. sporadic), hearing, or facial function with any SF-36 subscale ($p>.05$, Table 4).

However, increasing VS volume was associated with lower scores in the physical role, bodily pain, mental health subscales and the overall physical summary score. [Note: the bodily pain subscale is scored such that lower scores indicate more pain.] Controlling for all other variables, each additional cubic centimeter of tumor volume was associated with approximately a 0.5 point decrease in the affected HRQoL domains. In post-hoc bivariate analysis, patients who received VS surgery prior to baseline HRQoL assessment did not have significantly different SF-36 scores in any domain compared to patients with no prior surgery ($p>0.05$ for all).

Baseline HRQoL of children and adolescents with NF2

Normative SF-36 data is available only for individuals age 18 or older so a direct statistical comparison of the general population to data for the children and adolescents enrolled in the current study is not available. However, we report the baselines SF-36 data for these subjects so that this information may be available to other investigators. The mean scores for this group within each SF-36 subscale are presented in Table 3. We also present the mean scores of young adults (ages 18-24) in the general US population for comparison, as this is the closest age grouping for which US population norms are available. When comparing the child and adolescent SF-36 scores in this cohort to the closest available US normative scores, there were no obvious reported deficiencies in the quality of life of this small sample.

Short-term changes in HRQOL

SF-36 data was collected at baseline and then annually, providing the ability to compare scores over time for subjects who had at least two data points available for analysis. Of the original 73 adult subjects, 40 (55%) had both baseline and year 2 data available for comparison. The remaining 33 (45%) subjects either did not return for year 2 follow-up or were enrolled into the NF2NHS late enough that the study closed before they were eligible for a year 2 follow-up visit

There was a significant decline in physical role ($p=0.03$) and vitality ($p=0.04$) over the two-year period following enrollment, although general health remained the most impaired domain. 7/40 (17.5%) subjects received VS surgery during the 2 year observation period; change in SF-36 scores was not significantly different in any domain between patients with and without VS surgery. 20/40 (50%) of subjects experienced >20% growth in their larger VS; change in SF-36 scores was not significantly different in any domain between patients with and without VS growth.

15/40 (38%) patients decreased by >10 points (more than 1 standard deviation) in at least one physical subscale. 16/40 (40%) decreased by >10 (more than 1 standard deviation) in at least one mental subscale. Individual level changes in physical and mental summary scores were varied (Figure 1). 18/40 (45%) patients experienced HRQOL changes in the same direction for both physical and mental summary scales (i.e. both increased or both decreased), while 22/40 (55%) had discordant changes.

DISCUSSION

Radiographic measurements, audiometry, and House-Brackmann ratings of facial function are used by clinicians to objectively assess disease severity in patients with NF2. However, it is unknown whether these clinical measures correlate with patient-reported HRQoL. In this study, we analyzed SF-36 scores from 81 subjects enrolled in the NF2NHS, the largest published cohort of individuals with NF2 to be assessed with this widely-utilized measure of HRQoL. We found significantly lower HRQoL for subjects with NF2 in most of the SF-36 subscales when compared to the matched US general population. Decreased HRQoL was observed in physical, social and mental domains, consistent with prior studies using the SF-36 and other measures.(4;6;7)

Our study did not reveal any correlation between reported HRQoL and objective functional measures, suggesting that better clinician-assessed hearing or facial function does not guarantee better HRQoL. These results parallel a prior study which showed objectively rated hearing and facial function were generally not associated with patient reported measures of emotional functioning (anxiety, depression, self-esteem, and perceived stress).(18) We also examined the effects of surgery and tumor growth on HRQoL, since these events commonly result in significant neurologic dysfunction in NF2 patients. However, we did not observe significant differences in baseline HRQoL between patients with and without prior VS surgery. Similarly, receipt of VS surgery or VS growth did not correlate with changes in any HRQoL domains. Larger VS volume at baseline was related to worse physical role performance, bodily pain, mental health, and overall physical summary score. The explanation for this finding could not be determined from the available data.

As reported in many patient populations, patient attributes such as coping skills, resiliency, and the availability of social support can moderate the effect of functional declines on

HRQoL.(19;20) These personal and social attributes can vary greatly from individual to individual, and are not necessarily related to disease severity or the presence of specific disease manifestations. We found that individuals did not always experience concordant changes in HRQoL subdomains over time, demonstrating that even patients with improved physical functioning may experience worse psychosocial functioning. (Figure 1). Thus, psychological, social, and/or emotional interventions may be beneficial to patients regardless of clinical disease severity. A pilot intervention focused on increasing coping skills and resiliency has already shown preliminary efficacy in improving HRQoL and psychosocial functioning in adults with NF2.(22)

Future studies of HRQoL in patients with NF2 are needed to confirm our findings and explore the relationship between tumor volume and HRQOL. An important consideration is the sensitivity of the SF-36 to the effects of the specific clinical domains we investigated. The SF-36 and other general HRQoL measure, may not adequately capture effects of hearing loss and facial weakness on difficulties in communication, social anxiety, and other areas of HRQoL important in NF2. For this reason, disease or symptom specific HRQoL measures, such as the NF2-specific NFTI-QOL(4) or the Penn Acoustic Neuroma Quality of Life Scale (PAN-QOL)(21) may be useful in future studies

Our results should be interpreted in light of some limitations. Our sample was drawn from large NF2 referral centers, and so may not be generalizable to all individuals with NF2. While subjects from multiple centers within the United States, United Kingdom, and Australia were included in this study, the algorithm used to generate norm-based scores is based solely on the US population. While this allowed consistent scoring across the entire study population, the application of US norms to patients from other countries could skew our results.

The available data could only support broad classifications of function; finer grained categories may reveal correlates of HRQoL which we were not able to detect.. Our sample size limited the number of clinical covariates we could use in multivariate models.

In conclusion, data from this prospective, multi-center study indicates that individuals with NF2 experience decreased HRQoL in physical, social, and mental domains. Clinicians providing comprehensive care for individuals with NF2 should assess HRQoL for all patients, even those with apparently mild or limited disease as assessed by current objective measures of hearing or facial function. Larger VS may be related to reduced HRQoL, although the mediators and potential psychological moderators of this relationship are unknown. future studies using general and disease-specific measures are needed to confirm our findings and further investigate HRQoL in patients with NF2.

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Table 1. Baseline characteristics of study cohort

	Adults n=73	Children n=8	All study patients n=81
Median age at baseline HRQoL evaluation	34 years (range, 18-78)	13 years (range, 10-16)	31 years (range, 5-78)
Median age at diagnosis	27.5 years	9.4 years	25.8 years
Median number of years since diagnosis	4.9 years (range, 0.3 – 14.8)	3.6 years (range, 0.2 – 6.5)	4.5 years (range, 0.2 –14.8)
Male gender - N (%)	38 (52%)	5 (63%)	43 (53%)
Inheritance – N (%) Familial Sporadic Unknown	 14 (19%) 51 (70%) 8 (11%)	 3 (38%) 4 (50%) 1 (12%)	 17 (21%) 55 (68%) 9 (11%)
Prior Vestibular Schwannoma Surgery	48 (66%)	3 (38%)	51 (63%)

Table 2. Baseline quality of life in adults (age ≥18) with NF2 compared to age and gender matched US population norms.

SF-36 Scale	Adjusted Population Norm	NF2 adults (mean)	p-value
Physical Summary	52.0	49.7	**0.04**
Physical Functioning	52.2	47.8	**0.0005**
Physical Role	51.8	49.2	**0.04**
Bodily Pain	51.0	52.5	0.21
General Health	50.6	43.9	**<0.0001**
Mental Summary	49.1	46.0	**0.03**
Vitality	49.6	50.3	0.58
Social Functioning	50.3	46.1	**0.002**
Emotional Role	50.8	46.7	**0.01**
Mental Health	49.3	45.6	**0.01**

SF-36 norm-based scores range from 0-100, with a standardized population mean of 50, and standard deviation of 10. Higher scores indicate higher quality of life (for example, increased physical functioning, less pain).

Table 3. Baseline quality of life in children and adolescents with NF2 (n=8) compared to gender-adjusted norms for young adults in the general population

SF-36 Scale	Adjusted Population Norm (18-24 years old)	Children/Adolescents with NF2 (10-16 years old)
Physical Summary	52.5	55.1
Physical Functioning	52.7	54.8
Physical Role	52.3	53.6
Bodily Pain	50.9	56.0
General Health	51.2	49.8
Mental Summary	49.4	48.1
Vitality	50.3	53.5
Social Functioning	50.6	49.0
Emotional Role	51.2	52.7
Mental Health	49.4	49.9

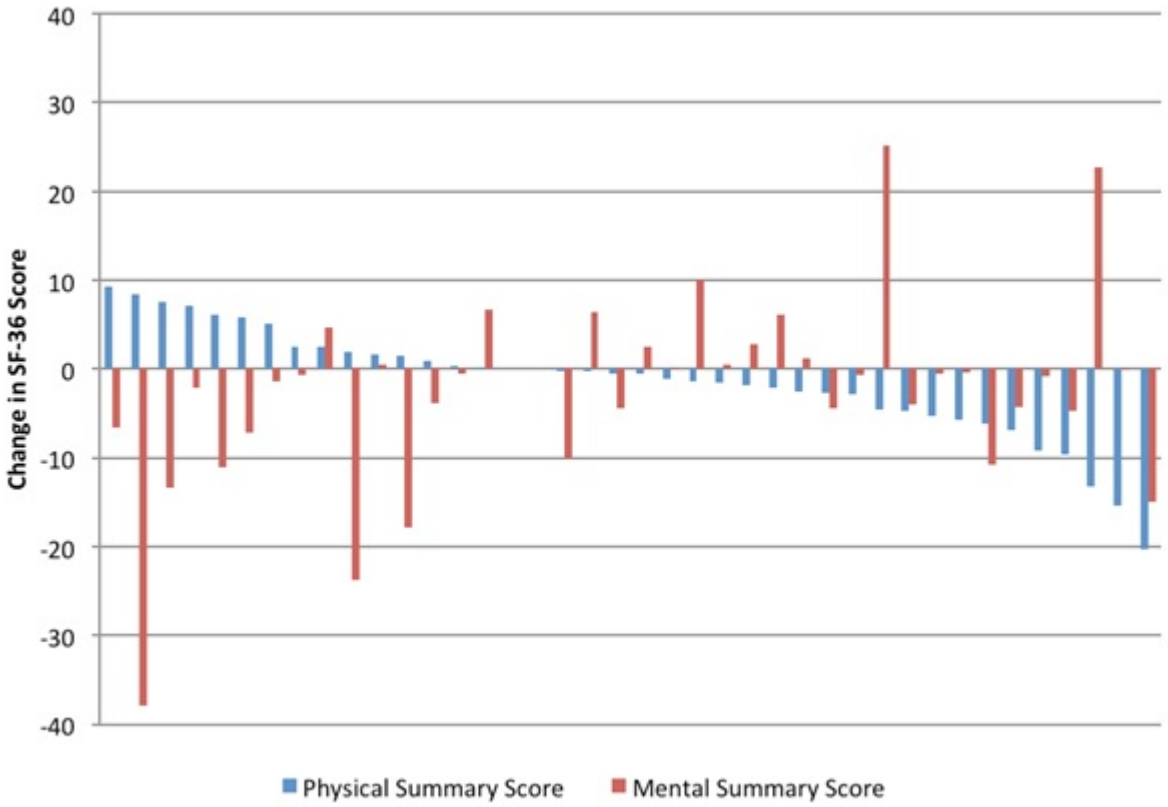
Table 4. Effect of demographic and objective clinical characteristics on SF-36 subscale scores

	Physical Functioning	Physical Role	Bodily Pain	General Health	Physical Summary
Intercept	45.76	53.64	52.37	40.27	47.74
Age (per year)	0.09	0.02	0.07	0.16	0.09
Female	1.32	-4.08	1.48	0.74	0.98
Familial Inheritance	-0.17	0.59	-0.90	2.97	-1.64
Hearing Loss	-0.46	-0.63	-0.79	-2.47	0.05
Facial Weakness	3.91	2.28	0.42	3.40	3.11
VS Volume (per 1 cc)	-0.26	-0.64**	-0.42*	-0.27	-0.36*

	Social Functioning	Emotional Role	Vitality	Mental Health	Mental Summary
Intercept	49.55	47.44	53.23	51.62	50.84
Age (per year)	0.07	0.10	0.05	0.02	0.05
Female	-5.53	-4.62	-3.68	-4.23	-6.23
Familial Inheritance	1.00	3.84	-1.36	2.39	3.01
Hearing Loss	-2.24	-1.49	-0.97	-3.92	-3.13
Facial Weakness	-1.86	0.66	-0.90	1.80	-0.88
VS Volume (per 1 cc)	-0.10	-0.40	-0.35	-0.50*	-0.34

Legend: VS = vestibular schwannoma. *$p \leq 0.05$, **$p \leq 0.01$

Figure 1. Absolute change in SF-36 score over two years.



Legend: Positive numbers represent an increase in function, while negative numbers represent a decrease in function. Each pair of bars represents an individual patient.

Supplemental Digital Content 1.

Centers participating in the NF2 Natural History Study

- House Ear Institute, Los Angeles, CA, USA (PI: William Slattery, III)
- Hôpital Beaujon, Paris, France (PI: Michel Kalamarides)
- Klinikum Nord Ochsenzoll, Hamburg, Germany (PI: Victor Mautner)
- Massachusetts General Hospital, Boston, MA, USA (PI: Mia MacCollin and Scott Plotkin)
- Mt. Sinai School of Medicine, New York, NY, USA (PI: Jeffrey Allen)
- Nagoya University, Nagoya, Japan (PI: Kiyoshi Saito)
- Ohio State University, Columbus, OH, USA (PI: D. Bradley Welling)
- Royal Victorian Eye and Ear Hospital, Melbourne, Australia (PI: Robert Briggs)
- St. Mary's Hospital, London, England (PI: Gareth Evans)
- University of Texas, Houston, TX, USA (PI: Joseph Chang)

*As only centers in English-speaking centers participated in the HRQoL portion of the study, patients from Hopital Beaujon, Klinikum Nord Ochsenzell and Nagoya University are not included in this report.