Quality of life among adult patients with neurofibromatosis 1, neurofibromatosis 2 and schwannomatosis: a systematic review of the literature

Quality of life among adult patients with neurofibromatosis 1, neurofibromatosis 2 and schwannomatosis: A systematic review of the literature

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Abstract:

The aim of this study was to review the literature on quality of life among adult patients with neurofibromatosis 1, neurofibromatosis 2 and schwannomatosis, and to identify the specific aspects of quality of life that were studied and reported in this population. We also set out to report predictors of quality of life. Published research reports were included if they described quality of life in this population and met methodological quality according to a list of predefined criteria. Eight studies (7 in NF1, 1 in NF2, 0 in schwannomatosis), conducted between 2001 and 2013, met inclusion criteria. The methodological quality of the 8 studies was mostly high according to ratings by predefined criteria. Most studies reported that patients with NF experience decreased quality of life when compared to the general population. Visibility and disease severity were strong predictors of skin-specific quality of life in NF1 patients. However, the majority of findings regarding predictors of quality of life were weak or inconclusive. Given the decreased quality of life in NF patients, it is important to examine more comprehensively the psychosocial factors in this population, especially in patients with NF2 and schwannomatosis. Mind body interventions that address these domains may provide comprehensive and efficacious long term treatment.

Key Words: neurofibromatosis 1, neurofibromatosis 2, schwannomatosis, quality of life,

Introduction

The neurofibromatoses (neurofibromatosis 1, neurofibromatosis 2 and schwannomatosis) are a group of genetic disorders that predispose patients to develop multiple nerve sheath tumors throughout the body. NF1 is the most common neurogenetic disorder, with an estimated birth incidence of 1:2700 [1]. Symptoms of NF1 include cutaneous manifestation, such as cafe-au-lait macules and cutaneous neurofibromas; bony abnormalities, such as pseudoarthrosis and scoliosis; learning disabilities; and gliomas [2]. NF2 is less common with an estimated birth incidence of 1:33,000 [1] and is characterized by the presence of bilateral vestibular schwannomas, which can lead to deafness, tinnitus, and balance problems [3]. Many patients with NF2 also have other tumors of the central nervous system such as meningiomas and spinal ependymomas.. Schwannomatosis likely has a prevalence similar to that of NF2 [4] and is characterized by the development of multiple schwannomas that may cause intractable pain [3].

Within the past decade, there has been increased awareness of the burden of disease in this population. While most NF-related tumors are histologically benign, each disorder can cause a significant decrease in quality of life in affected individuals.

The neurofibromatoses are heterogeneous diseases. Some individuals with NF1 live essentially normal lives, while others struggle with cosmetic disfigurement, neurologic dysfunction, psychological distress, and disability. [5, 6] Similarly, some patients with NF2 have life threatening symptoms from compression of vital structures, such as other cranial nerves and the brain stem, while others have more minor symptoms. In schwannomatosis, most individuals report pain, but only some develop pain-related disability. This heterogeneity of these diseases highlights the importance of identifying predictors of quality of life in this population. Quality of

life represents individuals' perception of their general well being, and typically includes emotional and physical components.

Within the past decade there has been an increased awareness of the mind-body connection in quality of life in patients with medical conditions, leading to a transition from a biomedical to a biopsychosocial model of care, where the medical and psychosocial factors of disease are assessed and treated concurrently. Although treatments for NF continue to be largely biomedical, research has started to assess quality of life in this population, as well as predictors of quality of life. The goals of this review were: 1) to identify the specific aspects of quality of life that are adversely affected in this population and have been reported in the research literature, and 2) to identify predictors of quality of life in this population. We were also interested in providing directions for future research, in particular with regard to the development of mind-body interventions and transitioning of care from a biomedical to biopsychosocial model of care.

Methods

We followed the PRISMA criteria [5] to identify, select, and determine eligibility of studies for inclusion in this systematic review.

Search strategy/identification

Reports of original research studies on the QoL of adults affected with NF1, NF2, or schwannomatosis were identified. Articles published in peer-reviewed journals as of February 27, 2013, were identified using literature searches of Pubmed and PsychINFO. Database searches were conducted using the terms neurofibromatosis, schwannomatosis, NF1, and NF2 in conjunction with one or more of the following key terms: quality of life, QoL, health related

quality of life, and well being. A total of 111 articles were identified, and after removing duplicates, the abstracts of 101 articles were screened.

Selection Criteria/Study Eligibility

Detailed inclusion and exclusion criteria were defined by the authors prior to reviewing abstracts (see Table 1). Eighty-eight studies did not meet inclusion criteria. Of these, 13 studies did not address individuals with NF, 48 did not address quality of life (29 reported only biomedical characteristics, 9 used cognitive/functional scales only, and 10 reported other findings), 16 addressed children only, 10 were case studies/or qualitative reports, and 2 were not in English. A total of 12 abstracts met inclusion criteria and the full-text was assessed further for eligibility. Four studies that did not measure quality of life with a standardized, reliable, and valid questionnaire were excluded, leaving 8 studies for inclusion in the review.

Data Extraction/Quality Assessment

Two investigators (A-M. V. and V.L.M) extracted data from the selected studies. Information was extracted on: study population, study design, QoL instrument, results, and key predictor variables. These authors then assessed the methodological quality of each study using a standardized 10-item checklist of predetermined criteria (Table 2). The checklist was a modified population-specific version of a previously established criteria list for systematic reviews [6,7]. Evaluation of the methodological quality yielded over 90% agreement between the two reviewers; all disagreements were resolved upon discussion.

Each item of a selected study that met our criteria was assigned one point. If an item did not meet our criteria or was described insufficiently, zero points were assigned. The highest possible score was 10. Studies scoring 70% or more of the maximum attainable score (e.g., score $\geq$7) were arbitrarily considered to be of "high quality". Studies scoring between 50%-70%

were rated as "moderate quality" (score 5-7). Studies scoring lower than 50% were considered "low quality" (score ≤4). Findings regarding predictors of quality of life were summarized according to level of evidence [8], (Table 3) and considered consistent if ≥70% of the studies that investigated a factor showed the same direction of the association.

Results

Study characteristics

A total of 8 studies were included [9-16]. All were cross-sectional surveys published between 2001-2013. Studies were conducted in variety of countries (2 in the US, 2 in Germany, 1 each in Belgium, the UK, Italy, and France). Of the 8 studies, 7 included patients with NF1, 1 included patients with NF2, and none included patients with schwannomatosis. These studies included a total of 1045 patients with NF1, 62 patients with NF2, and 30 healthy controls. Table 3 presents a summary of the studies' characteristics and findings, as well as their quality scores. The mean quality score for the studies was 7.1. Methodological shortcomings concerned mainly the lack of reported response rate and information on non-responders.

QoL measures

The validated instruments used to measure QoL in these studies can be categorized as general measures and diseases specific measures. The Medical Outcome Scale SF-36 is a 36-item scale is a general measure, constructed to survey general quality of life [17]. The SF-36 assesses eight health concepts: limitations in physical activities because of health problems; limitations in social activities because of physical or emotional problems; limitations in usual role activities because of physical health problems); bodily pain; general mental health (psychological distress and well-being); limitations in usual role activities because of emotional

problems; vitality (energy and fatigue); and general health perceptions. Other less known general QoL measures are: PedsQLNF1 Module-Adult (with physical, emotional, cognitive, and social functioning subscales) and Patient Benefit Questionnaire. The Skindex [18] is an NF1 disease specific 29 item measure design to determine skin specific quality of life, and it is used primarily in NF1 patients who have facial deformities as a primary marker. The measure has 3 subscales emotion, physical symptoms and functioning. The Dermatology Life Quality Index is a similar diseases specific measure. The Voice Handicap Index is a disease specific QoL measure assessing quality of voice. While the general measures give information on general functioning of a patient, the more specific measures provide a more clear relationship between particular symptoms (usually the more bothersome, like the skin deformities in NF1 patients) and quality of life.

QoL findings

Overall patients with NF reported lower general quality of life compared to the general population. The majority of studies used the SF-36 to assess general health-related QoL (e.g., not disease-specific QoL). In all these studies, impairment was found not only in the physical and mental summary scores, but also in the individual subscales suggesting difficulties in most aspects of QoL. Patients with NF1 also reported decreased skin-specific QoL (using the Skindex) compared to the general population. Voice-related quality of life was also found to be significantly lower compared to matched controls in one moderate quality study [11]. NF1 patients treated by specialists had significantly greater enjoyment of life and ability to lead a normal life than those treated by non-NF specialists in another moderate quality study [12].

Predictors of quality of life

The predictors of quality of life described below are listed in table 5. *Strong evidence* was found for the predictive value of visibility (cosmetic effects) and disease severity (medical complications and procedures) for skin-specific QoL in NF1 patients. There was strong evidence that neither visibility nor gender predicted general QoL. *Weak evidence* was found for the relationship between age and skin-specific QoL, with older patients having more impairment. There was also weak evidence for the association between general QoL and difficulties with social communication, communication with spouse/significant other, balance, and hearing patients with NF2. These difficulties were associated with lower QoL on selected subscales of the SF-36. *Inconclusive evidence* was found for the relationship between age, health status, treatment by a specialist, severity and general QoL, and between gender and skin-specific QoL.

Discussion

This systematic review summarizes the results of 8 studies on the quality of life of patients affected by NF1 (7 studies) and NF2 (1 study). No studies on schwannomatosis met inclusion criteria. All studies reported lower quality of life in patients with NF compared to the general population, regardless of the instrument used. When general QoL was assessed with SF-36, impairment was observed on all subscales: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. When a skin disease-specific QoL measure was used, impairment was found on each subscale of emotions, symptoms, and function. These results suggest that NF represents a considerable burden for patients, affecting all aspects of life.

In general, NF1 patients with more severe disease (e.g., medical complications) and visible (e.g., cosmetic effects) symptoms report worse skin specific quality of life. Although

inconclusive, there was some evidence suggesting that women affected by NF1 may have worse skin disease-specific QoL compared to men with NF1. Contrary to expectations, there was strong evidence that visibility of disease and gender did not predict general QoL. This suggests that perhaps psychosocial and coping factors may buffer the effect of visibility on general QoL.

Patients with NF1 often have visible external tumors that may be cosmetically disfiguring and associated with stigma and social exclusion [19]. As such, NF1 represents an assault on the self-image and lifestyle of patients. Patients may become self conscious and isolated, leading to an array of mental health difficulties. While reducing malformations is a priority in patients with NF1, repeated medical procedures are in of themselves stressful and imperfect, with inherent medical risks. In many situations, the risk of surgical complications outweighs the potential benefits of tumor excision. In the absence of a medical cure, psychosocial mind-body interventions to teach patients how to adjust to their condition are pivotal in improving quality of life in this population. This contention is similar to other chronic conditions for which there is no cure, such as chronic pain. However, more research on the specific psychosocial predictors of quality of life is necessary, as the majority of the findings from this review were weak or inconclusive, and mostly concerning only patients with NF1. Future research should assess psychosocial factors that have been found to be important in reports of QoL in other patients with chronic illness and cancer, such as coping, resiliency, depression, anxiety, and self efficacy [20,21]. If found to be important predictors of QoL, these can areas can become targets of future mind body interventions aimed at improving QoL in this population.

The results described in this review were partly inconclusive, despite use of validated QoL measures in each study. This was due to limited studies and/or poor methodology. Future research in this area should use reference groups of similarly aged individuals without NF and

reliable and valid QoL instruments. Replication of current studies in order to determine the conclusiveness of some results would also be beneficial to the field. In the meantime, we can implement strategies based on current knowledge about QoL in this population. For example, these studies indicate that severity and visibility are important predictors of skin specific QoL, and that generally women are more impaired in their skin diseases specific QoL. As such, these factors should be routinely assessed and accounted for by clinicians who treat patients with NF, and referrals for psychosocial treatments should be made for appropriate patients. Research on breast cancer shows that psychosocial intervention projects[22] resulted in both short and long term improved QoL and also decreased health care billings by 24% compared to women who did not attend these interventions. Future studies should explore whether interventions specifically designed for NF patients could yield similar results.

In sum, this systematic review shows that patients with NF suffer from impaired QoL. There is a relative lack of high quality studies in adult patients with NF, especially in patients with NF2 and schwannomatosis. There is a need for additional high quality research in this population, focused on assessing not only QoL, but also psychosocial predictors of QoL. This would allow development of mind body interventions integrated within biomedical practice, aimed at improving QoL in this population.

Conflict of interest

The authors declare that they have no conflict of interest.

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Table 1 Selection Criteria

Inclusion Criteria	**Exclusion Criteria**
Original research in peer-reviewed journal	Biomedical description only
Study population of patients with NF1, NF2, and/or schwannomatosis	Cognitive/emotional scales only
Includes adults (age 18+)	Qualitative study or case report
Use of a standardized, validated QoL measure	Article not available in English

Table 2. Criteria for assessing methodological quality of studies included in this review.

A	Socio-demographic and medical data described (e.g., age, race, employment, education, NF type)
B	Process of data collection clearly described (e.g., interviews, questionnaires)
C	Type of NF described (e.g. NF1, NF2, or schwannomatosis)
D	Results are compared between 2 or more groups (e.g., healthy populations, between patient groups, etc)
E	Participation and response rate reported and more than 75%
F	Differences between responders/nonresponders are presented when they exist.
G	Results are described also for physical, psychological and social domains when the QoL measure captures that.
H	Standard statistics (mean, median, ranges, SD) are present for the main study variables.
I	Patients signed an informed consent prior to study participation, and this was explicitly stated in the manuscript.
J	Selection of participants is adequately described.

Table 3. Level of evidence (adapted from Ariens et al, 2000)

Strong	Consistent findings (≥70%) in at least 2 high quality studies
Moderate	Consistent findings (≥70%) in one quality study and at least one moderate or low quality study
Weak	Findings in one high quality study or consistent findings (≥70%)in at least 3 or more low quality studies
Inconclusive	Inconsistent findings, or less than 3 low quality studies available
No evidence	No data present

Table 4. Overview of studies on quality of life among patients with NF1, NF2 and Schwannomatosis

Study	Study quality score	Participants	Age Mean (SD)	QoL measure	General Conclusion
Wolkenstein et al, 2001[9]	10	128 adults with NF1	40.4 (14.1)	SF-36; Skindex	Patients with NF have lower scores on the SF-36 compared to normal population. Severity of NF1 significantly predicted scores on SF-36 domains of physical functioning, bodily pain, general health perception and vitality but no Skindex domains. Visibility of NF1 significantly predicted lower scores on all subscales of the Skindex and on SF-36 domains of physical functioning, role-physical, social functioning, role-emotional, and mental health.
Kodra et al, 2009[14]	10	129 adults with NF1	37.7 (12.2)	SF-36; Skindex	NF1 patients had significantly lower scores on all SF-36 domains compared to general population. Increased visibility was significantly associated with all subscales of the Skindex but none of the SF-36.

Page et al, 2006[15]	9	169 adults with NF1	43 (11.7)	SF-36; Skindex	NF1 patients had significantly lower scores on all SF-36 domains compared to general population, with larger effects in patients with more severe complications. Increased disease visibility correlated with lower QoL as measured by the Skindex but not the SF-36. Increased disease severity was associated with worse scores on the physical functioning and symptom subscales of the Skindex and all subscales of the SF-36.
Neary et al, 2010[13]	9	62 adults with NF2	39.8 (15.1)	SF-36	NF2 patients had significantly lower scores on all subscales of the SF-36 compared to the general population. Significant correlations between all SF-36 subscales and patients' perceptions of difficulties with social communication and balance; selected subscales correlated with communicating with spouse/significant other, hearing difficulties, and mood change.
Langenbruch et al,	6	228 adults with NF1	44 (13)	Patient Benefit	NF1 patients treated by specialists had significantly greater enjoyment of life and ability to lead a normal life than those treated

2011[12]				Questionnaire	by non-NF specialists.
Granstrom et al, 2012[10]	5	228 adults with NF1	43.8 (13.3)	Dermatology Life Quality Index	Higher self-perceived disease visibility was significantly associated with decreased QoL. Body image (as measured by the insecurity/experience subscale of the Evaluation of the Own Body Questionnaire) partly mediated the effect of visibility on quality of life.
Cosyns et al, 2012[11]	5	29 adults with NF1, 30 healthy controls	35 (10.9)	Voice Handicap Index (VHI)	NF patients had significantly worse scores on the VHI compared to matched healthy controls. Voice quality, as measured by the Dysphonia Severity Index, did not correlate with VHI, but increased age predicted worse voice-related quality of life.
Nutakkiet al, 2013[16]	5	134 adults with NF1	40.2	PedsQLNF1 Module-Adult	Quality of life (including physical, emotional, cognitive, and social functioning subscales) significantly decreases as self-reported health status declines.

Table 5. Predictors of QOL in NF1

Possible predictor	Direction of Association	Strong evidence	Weak evidence	Inconclusive
NF1				
General QoL				
Visibility [16, 17]	No association	X		
Gender [16, 17]	No association	X		
Severity [11, 17]	Negative			X
Health status [18]	Positive			X
Age [11, 16, 17]	No consensus			X
Skin-specific QoL				
Visibility [11, 12, 16,17]	Negative	X		
Severity [11, 17]	Negative	X		
Age [16, 17]	Negative		X	
Gender [11, 16]	No consensus			X
Other QoL measures				
Severity and voice related QoL[13]	Negative			X
Treatment by a specialist and life enjoyment[14]	Positive			X
NF2				
General QoL				
Difficulties with social communication [15]	Negative		X	
Communicating with spouse/significant other [15]	Negative		X	
Balance [15]	Negative		X	
Hearing difficulties [15]	Negative		X	
Mood change [15]	Negative		X	

Supplemental Figure: Prisma 2009 Flow diagram