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Impact of Neurofibromatosis 1 on Quality of Life Using the Skindex-29 Questionnaire in a Spanish Population

Atallah Isis*, Ana M. Cieza Rivera, Carlos Lobato Fuertes, Tania Fernández-Villa, Vicente Martín
Department of Biomedical Sciences, University of Leon, Spain

ABSTRACT

Background: Neurofibromatosis type 1 (NF1), the most common genodermatosis, predisposes affected patients to melanocytic lesions and benign tumors. NF1 is associated with a considerable esthetic and functional burden that may negatively affect patients' quality of life (QoL).

Aim: This study aims to assess the clinical features of NF1 patients and evaluate their impact on QoL.

Methods: NF1 patients were identified from a public health database of a region in Spain. All patients underwent clinical and ophthalmological evaluation for NF1 features. QoL was measured with the Spanish version of the Skindex-29 questionnaire. Logistic regression was performed to identify possible determinants of quality of life.

Results: 40 patients fulfilling NF1 NIH diagnostic criteria were recruited (age 40.95 years ± 16.1 SD). The mean total Skindex-29 score was 14 ± 11 (emotions: 20 ± 18, symptoms 10 ± 11, functioning 9 ± 10). Women and NF1 patients with lower educational levels were associated with poorer quality of life scores. Itching, headaches, and sleep troubles were identified to negatively influence the quality of life of NF1 patients.

Conclusion: NF1 considerably influences the psychological well-being of NF1 patients. Some of those symptoms might be amenable to a therapeutic approach, potentially improving NF1 patients' quality of life if seeked.

Keywords: Quality of life; Skindex-29; Neurofibromatosis 1; NF1

INTRODUCTION

Neurofibromatosis type 1 (NF1; OMIM# 162200) is one of the most common autosomal dominant disorders with a prevalence of one in 2500 to 3000 individuals. It is characterized by the presence of café au lait spots, axillary freckling, Lisch nodules, dermal and/or plexiform neuro-fibromas, skeletal dysplasia, and optic gliomas [1]. As NF1 is a tumor suppressor gene, 99% of NF1 patients develop benign tumors such as cutaneous neurofibromas, starting from puberty and increasing in size and number with age, pregnancy, or stress [2-4] or plexiform neurofibromas which are congenital tumors that can bulk at any time during life [1]. NF1 patients are also at risk to develop malignancies such as neuro-fibrosarcomas, pheochromocytomas, or breast cancer. With complete penetrance and high variability, the progression of the disease is unpredictable [5,6]. In addition to the disease burden, NF1 patients may suffer from stigmatization due to the nature and visibility of the skin lesions, which might influence their physical, emotional, and social well-being. Studying the effects of NF1 on various aspects of QoL seems important to implement beneficial strategies to improve the QoL of NF1 patients.

The purpose of this study was to assess the quality of life of a phenotypically described cohort of NF1 patients living in a semi-rural region in the north of Spain by using the Skindex 29, a skin disease-specific quality of life questionnaire (QoL) [7,8] that have been used worldwide.

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Corresponding author Atallah Isis, Department of Biomedical Sciences, University of Leon, Spain, E-mail: maria-isis.atallah-gonzalez@chuv.ch

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METHODS

Study Population

NF1 patients were identified by using the database of the Public Health Primary Care system and the database from the Leon University Hospital (Spain) by looking for the following items "Neurofibromatosis", "Neurofibromatosis type 1", "dermal neuro-fibroma", "plexiform neuro-fibroma" and "neuro-fibrosarcoma". We identified 106 patients fulfilling one of the mentioned criteria. Patients with a diagnosis of neurofibromatosis type 2, carrying solitary tumors, or living outside the Leon public health area were excluded. 16 patients were already deceased. Patients were contacted by post and telephone. We were not able to be in contact with 18 patients and 14 patients refused to participate (**Figure 1**).

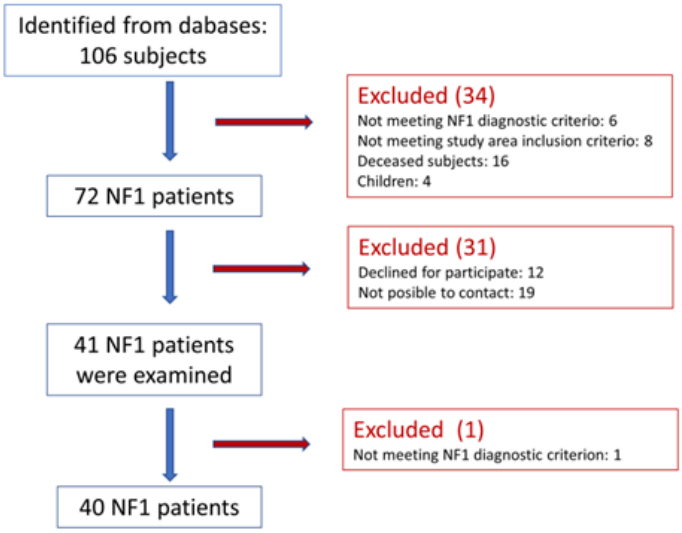

Figure 1: Flow diagram for patient recruitment.

We identified 45 patients with a diagnosis of NF1; four of them were children and were excluded from this study. 41 patients were enrolled in the study. NF1-expert clinicians and ophthalmologists examined all patients. A patient who did not fulfil the NF1 diagnosis criteria was excluded. Genetic analysis was available for 8 patients.

The Institutional Review Board and the Ethics Committee of Leon University Hospital approved the study protocol (approval number 1060).

Severity and Visibility Evaluation

The disease severity was assessed using the Riccardi scale [9] which has 4 degrees of severity with Grade 1, being the mildest form and Grade 4 being the more severe. In Grade 1, the patients have some of the diagnostic features of NF1 without any compromise of health and well-being. In Grade 2, the patients have some features that make disease evident without having an impact on their health and well-being. In grade 3, patients have features that can affect their well-being without significant compromise of health, and in grade 4, patients have a seriously compromised health and well-being in a permanent, unmanageable way.

The disease visibility was evaluated in fully dressed patients by using the Ablond scale [10] which has 3 degrees of severity. In grade 1, the disease is not visible with clothes. In grade 2, the patient presents some visible neurofibromas on the undressed body areas such as the face, neck, and hands or mild scoliosis. In grade 3, the disease is evident as the patient presents numerous visible tumors, disfiguring tumors, and severe complications such as severe scoliosis or cecity due to optic glioma.

Quality of Life Measurement Tool

The Spanish version of Skindex-29 [11], which was fulfilled by the patient during clinical evaluation, was used to measure the quality of life of NF1 patients. The Skindex-29 has 29 items distributed in 3 domains which represents three specific aspects of skin disease: physical symptoms (items 1, 7, 10, 16, 18, 23 and 26), functioning (items 2, 4, 5, 8, 11, 14, 17, 19, 21, 24, 28 and 29) and emotions (items 3, 6, 9, 12, 13, 15, 20, 22, 25 and 27). Each item is rated on a 5-point Likert scale (never, rarely, sometimes, often, all the time). Scale scores were calculated by averaging the responses to items of a given domain. A higher score indicated a greater effect of the disease.

Data Analysis

Descriptive statistics analysis was used for clinical features of the NF1 patient cohort. We used mean and standard deviation in quantitative variables as well as percentages in qualitative variables. T-tests and analysis of variance were used to compare scale scores in different clinical groups. Pearson correlation was used to compare scales. Logistic regression was performed to determine the factors associated with QoL. STATA 16 software was used for statistical analysis [12].

RESULTS

Sample Characteristics

40 patients were clinically evaluated and 38 performed an ophthalmological evaluation. The main clinical features and sociodemographic characteristics of the NF1 patients included in this cohort are summarized in **Table 1**. Detailed clinical characteristics are available in **Supplementary Table S1**. The mean age of NF1 patients was 40.95 (16.1 SD). 21 patients were women (52.5%). From the cutaneous point of view, the mean features were the presence of café-au-lait macules (97.5%), axillary or inguinal freckling (95%), cutaneous neurofibromas (80%), plexiform neurofibromas (43%) and hypopigmented (naevus anemicus) (8%). Thus, 37.5% of patients complained of pruritus.

Table 1: Sociodemographic and clinical features of the NF1.

	N	n	%
Sex			
Females	40	21	52.5
Males	40	19	47.5
Age (years)			
<35	40	17	42.5
35-54	40	14	35
>=55	40	9	22.5
Level of Education			

Undergraduate	33	14	42.4
Vocational education	33	13	39.4
University degree	33	6	18.2
Clinical Characteristics			
Six or more café au lait macules	40	39	97.5
Axillary and/or inguinal freckling	40	38	95
Two or more neurofibromas	40	32	80
Plexiform neurofibroma	40	17	42.5
Two or more Lisch nodules	37	29	78.4
Optic pathway glioma	40	4	10
Osseous lesions	40	20	50
Family history	40	20	50
Neurocognitive features	40	18	45
Central Nervous System	40	14	35
Short stature (<P3)	40	14	35
Macrocephaly (>P97)	40	5	12.5
Emphysema	40	1	2.5
Pruritus	40	15	37.5
Hypomelanic macules	40	3	7.5
Dizziness	40	12	30
Sleeping troubles	40	10	25
Headaches	40	9	22.5
Myomas	21	4	19
Malignancies	40	4	10

Disease Severity/Disease Visibility

Results of skindex disease, Ablond Index, and Riccardi severity scores are resumed in **Table 2**. Most patients had mild or minimal severity status (52.5%) and moderate disease visibility (42.5%).

Skindex

The mean skindex score was of 19.1 ± 16.2 SD (women 22.7 ± 13.5 DS; men 15.1 ± 18.2 SD; p=0.144). Emotions items (10.0 ± 8.7 SD) scored higher than symptoms (3.5 ± 3.8 SD) or functioning (5.7 ± 6.7 SD). **Figure 2A** shows the results stratified by sex and domain (emotions, physical symptoms, and functioning). We observed a strong association between the emotion and functioning scores (p<0.001) and a weaker association between the physical symptoms and the functioning scores (p=0.010). The 5 items with a higher score were "I worry that my skin condition might get worse" (84 points, emotion), "My skin made me feel depressed" (44 points, emotion), "My skin affects my social life" (43 points, functioning), "I am ashamed of my skin condition" (42 points, emotions) and "My skin itches" (40 points, symptoms) (**Table 2**).

Table 2: Skindex-29 results in NF1 patients stratified by age group, disease visibility (Ablond's score) and disease severity (Riccardi's score).

	N	n	%	Emotions Mean (SD)	Physical Symptoms Mean (SD)	Functioning Mean (SD)
Sex						
Females	40	21	52.5	12.2 ± 8.3	3.7 ± 3.5	6.7 ± 5.9
Males	40	19	47.5	7.4 ± 8.7	3.2 ± 4.2	4.5 ± 7.5
p value[a]				0.082	0.709	0.32
Age (years)						
<35	40	17	42.5	9.9 ± 7.6	2.2 ± 2.3	5.4 ± 6.7
35-54	40	14	35	10.8 ± 10.9	5.5 ± 4.5	6.4 ± 8.2
>=55	40	9	22.5	8.8 ± 7.6	2.7 ± 3.0	5.0 ± 4.2
p value[a]				0.871	0.036	0.883
Ablond's score						
Grade 1	40	12	30	9.2 ± 7.6	2 ± 3.0	3.9 ± 4.5
Grade 2	40	17	42.5	10.6 ± 9.1	4.2 ± 4.2	6.7 ± 8.4
Grade 3	40	11	27.5	9.7 ± 10.0	3.8 ± 3.7	5.9 ± 5.9
p value[b]				0.904	0.279	0.551
Riccardi's score						
Grade 1	40	5	12.5	5.2 ± 4.2	2.6 ± 1.7	2.0 ± 3.4
Grade 2	40	16	40	8.8 ± 7.5	3.4 ± 4.5	3.9 ± 4.5
Grade 3	40	15	37.5	12.5 ± 10.5	3.9 ± 4.0	8.9 ± 8.6
Grade 4	40	4	10	11.0 ± 9.2	3.0 ± 2.2	5.3 ± 5.7
p value[b]				0.381	0.927	0.105

[a]Contrast data by T-Student. [b]Contrast data by ANOVA.

Women showed higher scores on emotions items than men (12.2 ± 8.3 vs. 7.4 ± 8.7; p=0.082). However, Skindex scores on symptoms and functioning were similar for both sexes. Aging was not correlated with increased scores on emotions, functioning, or physical symptoms. However, the physical dimension was significantly impacted in NF1 patients between 35 and 54 years (p=0.036) (**Figure 2B**). NF1 patients with higher visibility and severity scores did not show any statistical difference in Skindex scores.

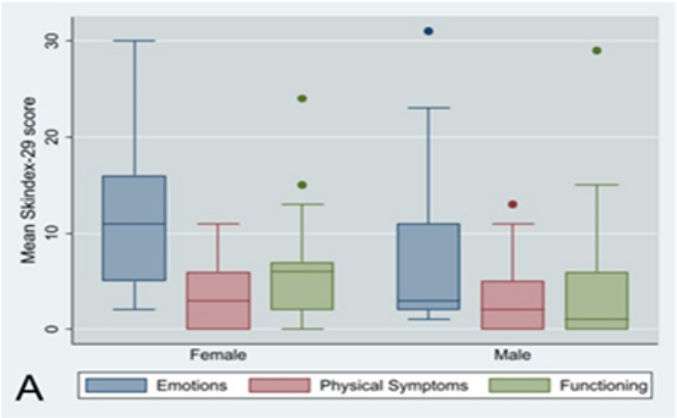

Figure 2A: Mean Skindex-29 scores by sex and domains.

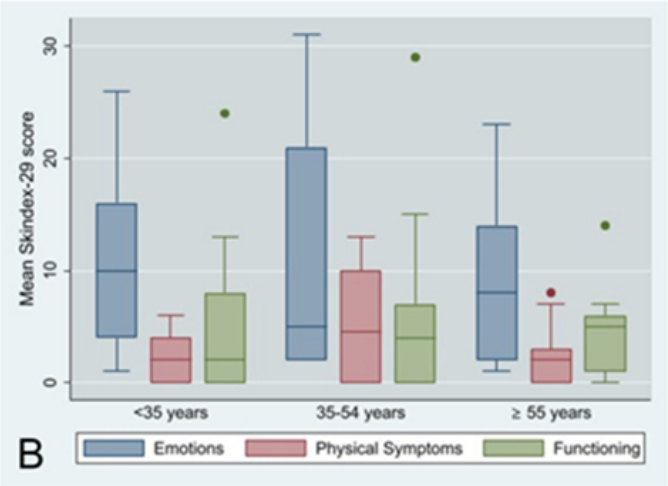

Figure 2B: Mean Skindex-29 scores by age groups and domains.

Logistic regression identified higher scores on emotion domain of skindex-29 in patients with lower educational levels (p=0.051) and higher head circumference (p=0.016) which was also associated with higher scores on the functioning domain (p=0.032). Patients with pruritus and sleep troubles have a significant impact on symptoms domain (p=0.001 and 0.036, respectively). The sleep troubles seem to affect functioning (p=0.052) and it is associated with headaches (p=0.01).

DISCUSSION

Improving the quality of life of our patients is an important objective for all physicians and health workers. This is even more important in patients with rare disorders as they must frequently deal with ignorance and incomprehension.

To date, only a few studies have assessed the quality of life in NF1 patients [13-19]. Compared to prior studies, our patients reported a lower impact of NF1 on their quality of life as their scores were lower than in prior reports [13,17]. This could reflect differences in enrollment, population, disease staging, demographic differences, the health care system, and study design. All NF1 patients included in this study were identified from a primary care unit or reference hospital in a semi-urban area where patients are followed mainly by general practitioners and dermatologists and may therefore be more representative of the general population than patients followed in a Neurofibromatosis clinic. Furthermore, Spain has a public health System, which might contribute to facilitating access to medical care and lessening the financial burden of the disease and the impact on disease perception. Expert physicians and not the patient himself (as in previous studies) assessed Ablon's visibility and Riccardi's severity scores; patients could be biased by their own disease perception. The patient fulfilled the skindex-29 at the same time point. The main limitation of this study is the small number of NF1 patients enrolled which limited the statistical power of some findings.

Skindex-29 revealed that NF1 women and patients with lower educational levels suffer more emotionally than other patients with the same condition do. We also observed a strong association between the emotions and functioning scores on skindex-29, which might indicate that these two domains are functionally related. Therefore, clinicians should be more attentive to the emotional status of NF1 patients and be more prone to use depression-screening questionnaires such as the PHQ-9 [20,21] or the generalized anxiety disorder-7 item scale (GAD 7) [21,22]. Depression, described in up to 55% of NF1 [23] patients, has been associated with pain intensity and pain interference [24]. Improving depression by mind-body based interventions [25] and/or pharmacological treatment [26] may reduce pain interference in the daily lives of patients. Surprisingly, logistic regression found an association between macrocephaly and higher emotion scores. Macrocephaly (without hydrocephaly), observed in 37,5% to 50% [27,28] of NF1 patients, has mostly been attributed to increased white matter volume by magnetic resonance imaging [29,30] and was generally not related to cognitive outcomes [29]. However, larger left putamen and larger total white matter volume were associated with more social problems and poorer executive functioning [31] which could, at least partially, explain our findings.

Not surprisingly, the frequency of the main clinical features of NF1 patients enrolled in this study was similar to previous literature reports [1,32,33]. However, it is interesting to note that about 1/3 of the patients were complaining of pruritus and ¼ of dizziness, headache, or sleeping troubles. Although those are not life-threatening features, they seem to have an impact on the QoL of NF1 patients. Prior studies described pruritus in about 20% to 35% of NF1 patients [19,20] and it was described as the more bothersome symptom of NF1 in 14% of patients [2]. Pruritus seems to have neuropathic features [34] and is mainly localized in one or 2 neurofibromas and could therefore be alleviated by topical treatment [22] or neurofibroma removal by surgery, carbon dioxide laser [35,36], or electro-desiccation [37].

Migrainous and non-migrainous headaches are frequent in NF1 patients [38,39]. Migraine can be observed in 34 to 83% of patients with NF1, affecting significantly their quality of life [38,39]. Therefore, patients should receive specific anti-migraine treatment. Sleep troubles such as parasomnias, difficulties initiation sleep, early morning awakenings, and excessive sleep/wake transition are also frequently described in NF1 patients [40]. A sleep study performed on 114 NF1 patients identified 69% as being "poor sleepers" and 20% with excessive day sleepiness [40]. As sleep disturbance is a very common migraine trigger, it might be responsible for some of the headaches described in our patients and may predispose them to depression. Therefore, NF1 patients should benefit from the classical diagnostic and therapeutic strategies [41,42] (**Figure 3**).

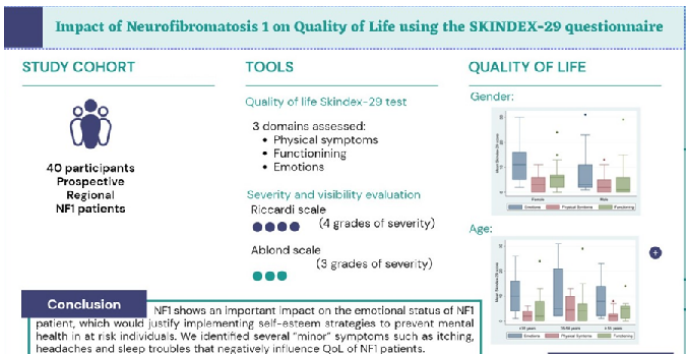

Figure 3: Impact of neurofibromatosis 1 on Quality of life using the SKINDEX-29 Questionnaire.

CONCLUSION

This study highlights the impact of NF1 on the quality of life in a cohort of patients coming from a public health primary care area. NF1 shows an important impact on the emotional status of NF1 patients, which would justify implementing self-esteem strategies to prevent mental health in at-risk individuals. Thus, we identified several symptoms such as itching, headaches, dizziness and sleep troubles that negatively influence the QoL of NF1 patients. As those symptoms are not perceived as NF1-related, patients may not mention them. Therefore, clinicians should actively seek for those symptoms to treat them and improve the QoL of their NF1 patients.

HOW THIS FITS IN WITH QUALITY IN PRIMARY CARE

What do we know?

Neurofibromatosis type 1 is a rare disease with high visibility and variable severity which impact self-esteem and quality of life (QoL) and predisposes patients to pain, anxiety and depression.

What does this paper add?

This study increases the knowledge concerning the factors affecting QoL in NF1 patients. We observed that female patients, low-educated patients and macrocephalic patients scored higher on the emotional dimension of the skindex-29 and could therefore be more at risk of depression. We also pointed out some "minor symptoms" that negatively influence NF1 patients QoL such as itching, sleep troubles, dizziness or headache.

Clinicians in charge of NF1 patients should be aware of those symptoms to treat them and improve the QoL of their patients. Thus, self-esteem strategies should be implemented in the follow-up guidelines of NF1-patients to prevent mental health in at-risk individuals.

ETHICS STATEMENT

The Ethical institutional review board Committee of the Complejo Asistencial Universitario de León (approval number 1060) approved the study protocol. All study participants provided written consent.

CONSENT FOR PUBLICATION

All patients provided their written consent to participate in this publication.

AVAILABILITY OF DATA AND SUPPORTING MATERIALS SECTION

The authors confirm that the data supporting the findings of this study are available upon request.

COMPETING INTERESTS

All authors state that they have no competing interests to declare. None of the authors accepted any reimbursements, fees, or funds from any organization that may in any way gain or lose financially from the results of this study.

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AUTHOR'S CONTRIBUTION

IA conceived, planned, and conceptualized the study. IA, ACR, and CLF contributed to acquiring and interpreting clinical data. TFV, IA, ACR, and VM performed the statistical analysis. IA wrote the initial manuscript. All authors critically reviewed, edited the manuscript, and approved the final version as submitted.

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COMPETING INTEREST

The authors declare that they have no competing interests.

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