Quality-of-Life Impairment in Neurofibromatosis Type 1

A Cross-sectional Study of 128 Cases

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Background: Neurofibromatosis type 1 affects quality of life (QoL) through association with severe complications, impact on cosmetic features, and uncertainty of the effects of the disorder.

Objective: To evaluate the impact of the severity and visibility of neurofibromatosis type 1 on QoL.

Design: Monocenter, cross-sectional study.

Setting: One French academic dermatological and neurofibromatoses clinic.

Patients: A total of 128 adult patients with neurofibromatosis type 1.

Main Outcome Measures: Evaluation of severity and visibility using, respectively, the Riccardi and Ablon scales. Evaluation of skin disease–specific and general QoL using, respectively, Skindex-France and SF-36 (Short Form 36 health survey) profiles controlled for sex, age, severity, and visibility.

Results: In a multiple regression model controlling for sex, age, and visibility, visibility remained independently associated with the alteration of 3 aspects of the skin disease–specific QoL (Skindex-France): emotions, physical symptoms, and functioning ($P_{.03}$, $P_{.009}$, and $P_{.002}$, respectively). Patients with more severe neurofibromatosis reported more effects on the following domains of their general health QoL (SF-36): physical function, bodily pain, general health perception, and vitality ($P_{.006}$, $P_{.03}$, $P_{.01}$, and $P_{.04}$, respectively).

Conclusions: Neurofibromatosis type 1 has a significant impact on QoL through alteration of health and appearance. The consequences of visibility and severity from the viewpoint of patients can be evaluated using Skindex and the SF-36, respectively.

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PATIENTS AND METHODS

PATIENT SAMPLES

Informed consent was obtained from 170 adult patients having NF1, according to the US National Institute of Health consensus statement,1,2 and registered in the database of our neurofibromatosis clinic, the Réseau NF. The severity and visibility of NF1 in these 170 patients had been evaluated within the past year, and data were available in the Réseau NF database. This panel was chosen to be representative of a previously described cohort: adult patients; man-woman ratio, 0.75; and severity grades 1 through 4 (grade 1, 5%; grade 2, 25%; grade 3, 50%; and grade 4, 20%). Patients who returned their informed consent were enrolled in the study. One questionnaire including 2 measures of QoL (Skinindex-France and SF-36) were mailed to these patients, who were asked to answer the questionnaires within a week of receipt. The SF-36 responses of these patients were compared with those of a normative sample of 3656 subjects representative of the French population.

MEASURES

Severity and Visibility Evaluation

The Riccardi scale was used to evaluate the severity of the disease. Briefly, grade 1, or minimal NF, means the presence of few features of NF with no compromise of health or well-being. Except for café au lait spots and iris Lisch nodules, grade 1 is most accurately defined by the absence of features, while grades 2 to 4 are predicated on the presence of specific features and an ordered level of compromise. Grade 2, or mild NF, reflects the presence of enough stigmata to make the disease obvious and a source of concern, but without significant compromise of health. For example, the patient may exhibit facial café au lait spots or a modest number of cutaneous or deep neurofibromas. In grade 3, or moderate NF, there is unequivocal compromise of health and well-being, but the compromise can be reasonably well managed, is not intractable, and will not invariably lead to a shortened life span. Because many features of NF can lead to this level of clinical problems, the category of severity grade 3 is necessarily broad, spanning a relatively large age range. Grade 4, or severe NF, indicates the presence of serious compromise that is intractable, is managed or treated only with difficulty, or is associated, at least statistically, with a shortened life span. Mental retardation, drug-resistant seizures, brain tumors, and malignant tumors contribute to this category of complications.

The Ablon scale was used to evaluate the visibility of the disease. Briefly, the ratings are based on appearance of the person fully dressed and how readily physical symptoms could be perceived in impersonal interaction. It should be noted, however, that many persons who display no tumors on areas visible in normal street clothes have numerous tumors or café au lait spots on the torso that would be apparent in physically intimate situations, and may gravely affect sexual behavior. Grade 1 on the Ablon scale indicates a mild case: essentially no tumors are visible outside

SAMPLE CHARACTERISTICS

Of the 170 patients asked to participate in this study, 135 gave their informed consent, and 128 answered the first mailing. These 128 patients with NF1 were not different from nonresponders (data not shown). They ranged in age from 15 to 73 years (mean±SD, 40.4±14.1 years) and were asked to answer the questionnaires within a week of receipt. The SF-36 responses of these patients were compared with those of a normative sample of 3656 subjects representative of the French population.

RESULTS

Of the 170 patients asked to participate in this study, 135 gave their informed consent, and 128 answered the first mailing. These 128 patients with NF1 were not different from nonresponders (data not shown). They ranged in age from 15 to 73 years (mean±SD, 40.4±14.1 years) (Table 1). Most patients were women (man-woman ratio: 0.71). Most patients had mild or moderate NF1. The NF1 visibility was equally distributed. The severity and the visibility of NF1 were similar in women and men (nonparametric Wilcoxon test severity mean rating, 2.68 vs 2.55; P=.39; visibility mean rating, 1.88 vs 1.83; P=.73). There was no difference in severity between different age categories (nonparametric Wilcoxon test, P=.61). The visibility increased significantly with age (nonparametric Wilcoxon test, P=.005).

SKIN-DISEASE-SPECIFIC QoL MEASURED WITH SKINDEX-FRANCE

The Figure shows the Skinindex-France scores of patients with NF1. The effects of NF1 on 2 aspects of skin disease—specific QoL were different between men and women. The effects of NF1 were similar on the functioning aspect for both men and women (analysis of variance, P=.43), but they were significantly greater on emotions and physical symptoms for women than for men (analysis of variance, P<.001 and P=.01, respectively). The sex effects did not persist when we controlled for sex, age, and visibility. The effects of NF1 on skin disease–specific QoL were somewhat greater in older patients, although the difference did not reach statistical significance.

Patients with more severe NF1 did not report more effects on their skin disease–specific QoL. However, patients with more visible NF1 reported more effects on each aspect of their QoL (emotions, physical symptoms, and functioning) (analysis of variance; P=.003, P=.001, and P<.001, respectively) (Table 2). In a multiple regression model controlling for sex, age, and visibility, visibility remained independently associated with the 3 specific aspects of their skin disease–specific QoL: emotions, physical symptoms, and functioning (analysis of variance; P=.03, P=.009, P=.002, respectively).

GENERAL HEALTH QoL MEASURED WITH SF-36

Our 128 patients with NF1 were compared with a normative sample of 3656 subjects representative of the French population (Table 3) who had answered the SF-36 questionnaire. For all domains of the SF-36 profile, patients with NF1 had significantly lower scores than the normative sample (t test using the Welch correc-
of normal clothing areas; gait and posture appear unremarkable when casually observed (this allows for heavy coating of neurofibromas on the body and some minor skeletal symptoms). Grade 2 indicates a moderate case: some tumors appear on the neck, face, and hands, and mild scoliosis or other skeletal features are present but without a noticeable limp. Grade 3 indicates a severe case: numerous tumors appear on the face; optic glioma (tumor) affects sight and the eye socket; severe scoliosis or skeletal features are present causing a noticeable limp.

Clinical information necessary to score severity and visibility was obtained from the database of the Réseau NF.

For this purpose, the information had been prospectively collected by 2 of us (P.W. and J.Z.). Final scoring was made by the first author (P.W.).

QoL Evaluation

Skin-disease-specific QoL was measured using Skinindex-France, the French version of a self-administered, 29-item questionnaire. Results were reported as 3 scale scores representing 3 specific aspects of QoL (emotions, physical symptoms, and functioning). Scale scores are the mean of responses to the items included in the scale. Scores are transformed to percentages, and higher scores indicate greater effects of skin disease on QoL. The cross-cultural adaptation in French of the Skindex was conducted using published guidelines. Psychometric analyses performed on this data set provide preliminary validation information on Skinindex-France. Overall, the acceptability of the questionnaire was good, with a low rate of missing data (<5%). The low rate of extreme responses (ceiling and floor effects <20%) indicates that the Skinindex-France questionnaire takes into account the range of health problems perceived by patients with NF1. Multitrait analyses confirmed that the underlying criteria of scale score calculation were met and that the scores were sufficiently reliable to allow group comparisons (Cronbach α coefficient: emotions, .95; physical symptoms, .86; and functioning, .94)(test-retest Spearman r: emotions, 0.92; physical symptoms, 0.84; and functioning, 0.90).

General health QoL was measured using the French version of SF-36, a self-administered, 36-item questionnaire. This instrument assesses the following 8 health domains: physical function, limitations because of physical problems, limitations because of emotional problems, social function, mental health, energy, pain, and health perception. Scores are transformed to percentages, and lower scores indicate greater effects of the disease on QoL.

Sociodemographic information was obtained using the patient questionnaires.

STATISTICAL ANALYSIS

Scale scores of patients in different clinical groups were compared using independent t test and analysis of variance. Non-parametric Wilcoxon tests and t tests using Welch correction were used when appropriate. Multiple linear regression was used to analyze Skinindex-France and SF-36 scores while controlling for sex, age, severity, and visibility.

Through its complications and impact on cosmetic features, NF1 has a major adverse effect on patients’ lives. The complications make up the severity of the disease; the cosmetic features, its visibility. Both severity and visibility may have consequences on the QoL of patients, affecting both health and appearance. Psychiatric and social aspects of NF1 were first studied by Samuelsson and Riccardi14 in Gothenburg, Sweden. In this work, patients with NF1 were asked to talk about their conditions, and the authors began to delineate the spectrum of adverse social and behavioral consequences of NF1. The burden of NF1 linked to its self-perception has been highlighted by interviews of patients.3,13: NF1 constitutes an assault on the self-image and lifestyle. Even though interpretation of patients’ interviews is absolutely necessary for understanding patients’ experiences, tools are now available to measure accurately how the QoL of patients is affected. In our study, we examined skin disease–specific and general health QoL in a sample of adult patients with NF1 representative of our hospital-based cohort. The effects of NF1 were significant in both aspects.

We emphasize 3 findings from our study. First, patients with NF1 reported an effect in all aspects of skin disease–specific QoL, but the emotional effect was the greatest. Moreover, they reported an effect in all domains of general health QoL.

Second, patients with more visible NF1 reported significantly greater overall effects on their skin disease–specific QoL, but skin disease–specific QoL was not affected by overall severity of the disease. On the other hand, in multivariate analysis, patients with more severe NF1 reported significantly greater effects on their general QoL. Therefore, QoL evaluation of patients with NF1 should include 2 measures: (1) a measure of skin disease–specific QoL (Skinindex) that is correlated to its visibility and (2) a measure of general QoL (SF-36) to appreciate the impact of the severity. This finding is interesting because one of the primary manifestations of NF1 is the presence of neurofibromas. External neurofibromas may be cosmetically disfiguring and thus cause considerable stigma leading to social exclusion.14 Reducing deformity is a subjective priority in adult patients with NF1, whatever the objective severity of NF1 in a particular patient. Indeed, in a previous study on NF1,15 no signifi-
cant correlation was found between the medical classification of severity and the subjects’ own perception. This apparent discordance was linked to the lack of knowledge about the severe complications of NF1, but also highlighted the impact of the cosmetic features that may be of great importance to the affected person and not taken into full account by the medical classification scale. In patients who graded themselves more severely affected than the score of the medical classification scale indicated, there was a significant association with expression of fears about the appearance of the lumps and about attempts to hide them. Cosmetic factors seem to play an important part in the perception of severity. Neurofibromatosis 1 constitutes an assault on the self-image mainly because of its effects on appearance. Our study confirmed these different aspects using the objective instruments of QoL measurement.

Third, patients with the most visible NF1 reported emotional effects of their skin condition. This impact was similar in magnitude to those reported in the literature for patients with psoriasis, which is traditionally regarded as a skin condition causing significant disability.9,10,16 On the other hand, in the NF1 group of patients, impact of the disease seemed slightly lower on symptoms and higher on functioning than in the psoriasis group.

Two methodological considerations of this study must be kept in mind. First, our patients with NF1, if they are representative of our hospital-based cohort, are probably not representative of the reality of NF1 in the general population. Indeed, patients with NF1 seen at our neurofibromatosis clinic are more likely to have a greater impact on their QoL, this impact leading to a referral center.

Table 1. Sociodemographic and Clinical Characteristics of 128 Patients With NF1*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>75 (58.6)</td>
</tr>
<tr>
<td>Male</td>
<td>53 (41.4)</td>
</tr>
<tr>
<td><strong>Age categories, y</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;18</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>18-24</td>
<td>17 (13.3)</td>
</tr>
<tr>
<td>25-34</td>
<td>30 (23.4)</td>
</tr>
<tr>
<td>35-44</td>
<td>32 (25.0)</td>
</tr>
<tr>
<td>45-54</td>
<td>27 (21.1)</td>
</tr>
<tr>
<td>55-64</td>
<td>12 (9.4)</td>
</tr>
<tr>
<td>65-74</td>
<td>8 (6.3)</td>
</tr>
<tr>
<td><strong>NF1 severity, Riccardi scale</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>12 (9.4)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>44 (34.4)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>52 (40.6)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>20 (15.6)</td>
</tr>
<tr>
<td><strong>NF1 visibility</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>51 (39.8)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>44 (34.4)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>33 (25.8)</td>
</tr>
<tr>
<td><strong>Level of education reached</strong></td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>16 (12.5)</td>
</tr>
<tr>
<td>Primary school</td>
<td>20 (15.6)</td>
</tr>
<tr>
<td>Secondary school</td>
<td>58 (45.3)</td>
</tr>
<tr>
<td>College</td>
<td>26 (20.3)</td>
</tr>
<tr>
<td>University degree</td>
<td>19 (14.8)</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>9 (7.0)</td>
</tr>
<tr>
<td><strong>Employment status</strong></td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>18 (14.1)</td>
</tr>
<tr>
<td>Employment full or part time</td>
<td>73 (57.0)</td>
</tr>
<tr>
<td>Retired</td>
<td>12 (9.4)</td>
</tr>
<tr>
<td>Unemployed and looking for work</td>
<td>7 (5.5)</td>
</tr>
<tr>
<td>Caring for home or family</td>
<td>6 (4.7)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (9.4)</td>
</tr>
</tbody>
</table>

*NF1 indicates neurofibromatosis type 1.

Table 2. Visibility Measured With Ablon Index and Skin-Disease-Specific Quality of Life Measured With Skindex-France in Patients With NF1*

<table>
<thead>
<tr>
<th>Skindex-France Characteristic</th>
<th>Grade 1 (n = 51)</th>
<th>Grade 2 (n = 44)</th>
<th>Grade 3 (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotions</td>
<td>22.2 ± 22.5</td>
<td>37.2 ± 26</td>
<td>39.9 ± 29</td>
</tr>
<tr>
<td>Physical symptoms</td>
<td>14.6 ± 13.8</td>
<td>23.5 ± 19</td>
<td>29.8 ± 24.5</td>
</tr>
<tr>
<td>Functioning</td>
<td>12.7 ± 18</td>
<td>28.3 ± 23.2</td>
<td>30.2 ± 26</td>
</tr>
</tbody>
</table>

*Data are mean ± SD scores. NF1 indicates neurofibromatosis type 1.
†Patients with more visible NF1 reported more effects on emotions, physical symptoms, and functioning (analysis of variance; \( P = .003 \), \( P = .001 \), and \( P < .001 \), respectively).

Table 3. Quality of Life of 128 Adult Patients Measured With SF-36 Compared With a Normative Sample of 3656 Subjects Representative of the French Population*

<table>
<thead>
<tr>
<th>SF-36 Characteristic</th>
<th>SF-36 Score</th>
<th>NF1 Patients†</th>
<th>Normative Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(n = 128)</td>
<td>(n = 3656)</td>
</tr>
<tr>
<td>Physical function</td>
<td>76.8 ± 26.4</td>
<td>84.5 ± 21.1</td>
<td></td>
</tr>
<tr>
<td>Role-physical</td>
<td>72.8 ± 39.1</td>
<td>81.3 ± 32.2</td>
<td></td>
</tr>
<tr>
<td>Bodily pain</td>
<td>65.3 ± 29.6</td>
<td>73.5 ± 23.7</td>
<td></td>
</tr>
<tr>
<td>General health perception</td>
<td>58.4 ± 23.0</td>
<td>69.2 ± 18.6</td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>49.7 ± 21.3</td>
<td>60.1 ± 18.1</td>
<td></td>
</tr>
<tr>
<td>Social functioning</td>
<td>70.4 ± 25.7</td>
<td>81.6 ± 21.4</td>
<td></td>
</tr>
<tr>
<td>Role-emotional</td>
<td>69.4 ± 39.4</td>
<td>82.2 ± 32.1</td>
<td></td>
</tr>
<tr>
<td>Mental health</td>
<td>56.4 ± 22.0</td>
<td>68.5 ± 17.6</td>
<td></td>
</tr>
</tbody>
</table>

*Data are mean ± SD scores. SF indicates short form; NF1, neurofibromatosis type 1.
†For all domains of the SF-36 profile, patients with NF1 had significantly lower scores than the normative sample (\( P < .05 \); \( t \) test using the Welch correction).
Table 4. Severity Measured With the Riccardi Index and General Health Quality of Life Measured With SF-36 in Patients With NF*  

<table>
<thead>
<tr>
<th>SF-36 Characteristic</th>
<th>Grade 1 (n = 12)</th>
<th>Grade 2 (n = 44)</th>
<th>Grade 3 (n = 52)</th>
<th>Grade 4 (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical function‡</td>
<td>95.8 ± 5.1</td>
<td>80.9 ± 19.9</td>
<td>74.8 ± 26.2</td>
<td>60.3 ± 36.8</td>
</tr>
<tr>
<td>Role-physical</td>
<td>91.7 ± 16.3</td>
<td>82.3 ± 32</td>
<td>67.8 ± 40.9</td>
<td>53.8 ± 48.9</td>
</tr>
<tr>
<td>Bodily pain‡</td>
<td>89.4 ± 18.5</td>
<td>66.9 ± 29.3</td>
<td>63.8 ± 26.4</td>
<td>51.7 ± 36.1</td>
</tr>
<tr>
<td>General health perception‡</td>
<td>71.2 ± 12.6</td>
<td>64.2 ± 23.4</td>
<td>54.8 ± 22.8</td>
<td>47.9 ± 23.0</td>
</tr>
<tr>
<td>Vitality‡</td>
<td>57.9 ± 17.5</td>
<td>52.9 ± 20</td>
<td>48.4 ± 21.9</td>
<td>40.3 ± 22.3</td>
</tr>
<tr>
<td>Social functioning</td>
<td>78.1 ± 23.9</td>
<td>70.2 ± 26</td>
<td>72.1 ± 25.4</td>
<td>60.6 ± 25.4</td>
</tr>
<tr>
<td>Role-emotional</td>
<td>75 ± 40.5</td>
<td>77 ± 36.4</td>
<td>65.4 ± 40.1</td>
<td>59.2 ± 42.7</td>
</tr>
<tr>
<td>Mental health</td>
<td>64.7 ± 22.5</td>
<td>55.4 ± 24.1</td>
<td>57.5 ± 20.5</td>
<td>50.4 ± 20.9</td>
</tr>
</tbody>
</table>

*Data are mean ± SD. SF indicates short form; NF1, neurofibromatosis type 1.  
‡Patients with more severe NF1 reported more effects on physical function, bodily pain, general health perception, and vitality (P = .006, P = .03, P = .01, and P = .04, respectively).

Even though our study does not claim to be an epidemiological study on QoL in the NF1 general population, severity and visibility scales allow a valid and standardized description of our sample. Nevertheless, our cohort was not different from those of population-based studies.17,18 Second, according to patient interviews,19 Skinex measured most dermatological effects of NF1, and SF-36 measured the most impact on general health. Nevertheless, expression by patients of worry about the genetics of the disease (ie, passing the condition on to children) was an important issue that is too specialized to be evaluated by these 2 generic questionnaires. This domain was not explored in our study targeted on skin manifestations, but it should be investigated in further studies.

One can recommend to physicians treating patients with NF1 to evaluate the severity and the visibility of the disease using the Riccardi and the Ablon scales, respectively; the consequences of severity and visibility from the viewpoint of patients should be evaluated using the Skinex and the SF-36, respectively.

In conclusion, our study confirms research conducted using other methods suggesting that NF1 has a significant impact on QoL through alteration of health and appearance. Our study highlights the importance of combining information from generic measures with information from instruments designed specifically for use in people with skin disease. Measures of QoL in patients with NF1, as in patients with other diseases, can supplement measures of clinical severity and visibility as a way to comprehensively assess the outcomes of disease and treatment. While serious and intractable complications are associated with this disease, a priority among patients is for cosmetic correction. Reducing deformity with dermatological and/or plastic surgery should not be neglected by physicians.

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REFERENCES