QUALITY OF LIFE AND PSYCHOLOGICAL ADJUSTMENT IN CHILDREN AND ADOLESCENTS WITH NEUROFIBROMATOSIS TYPE 1

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Objective To assess quality of life (QoL) and psychological adjustment in children and adolescents with neurofibromatosis type 1 (NF1).

Study design Forty-six patients with NF1 were investigated between the ages of 7 and 16 years (mean, 11.6 years), with children and parents used as informants. TNO-AZL Questionnaire for Children's Health-Related Quality of Life and Child Behavior Checklist scores were compared with healthy reference groups. Predictive values of sociodemographic variables, illness-related variables, and family-related variables for quality of life and psychological adjustment were assessed.

Results Most dimensions of QoL in NF1 children and adolescents were different from reference values. Deviations in the NF1 group were an impairment of motor, cognitive, and social functioning and a reduction of positive and negative emotions. Also, psychological adjustment in patients with NF1 was significantly impaired compared with normal subjects. Illness-related variables had a negative impact on the emotional domain of QoL. Good family relationships positively affected both QoL and psychological adjustment.

Conclusions QoL and psychological adjustment are impaired in children and adolescents with NF1. Illness-related variables and the quality of family relationships are important predictors. *(J Pediatr 2006;149:348-53)*

Neurofibromatosis type 1 (NF1) is a genetic disease of the central and peripheral nervous system caused by a mutation in a gene on chromosome 17. It is inherited in an autosomal dominant mode, with a high rate of new mutations and a prevalence of 1 in 3000 to 4000 individuals.[1] The symptoms of NF1 are progressive, unpredictable, and highly variable, ranging from differences undetectable by the untrained observer through mild esthetic disfigurement to life-threatening conditions. Defining features include café-au-lait spots, axillary freckling, Lisch nodules, cutaneous and plexiform neurofibromas, optic gliomas, pseudoarthrosis, and scoliosis or other skeletal abnormalities.[2] Complications can occur, including esthetic disfigurement, skeletal abnormalities, and a variety of benign and malignant tumors of the central nervous system.[1] The most common neurologic complications of NF1 in children and adolescents are cognitive impairments.[3] The diagnosis of attention deficit-hyperactivity disorder is common in children with NF1.[4]

The esthetic disfigurement and the physical and cognitive problems commonly associated with NF1 suggest a negative impact on the quality of life (QoL) and psychological adjustment of children and adolescents. One prior study confirms this suggestion for affected adults.[5] Little research, though, has focused on the psychological and social aspects of NF1 in children and adolescents. Although the self-concept of children and adolescents with NF1 was shown to be normal,[6] behavioral and social problems were reported.[7] Compared with unaffected siblings, children with NF1 showed more overall problem behaviors and internalizing and externalizing behavioral problems[7] as well as poorer social skills.[8] In a recent study assessing personality profiles, children and adolescents with NF1 are described as less conscientious, less emotionally stable, less open for new experience, less active, more extravert, more dependent, and more irritable.[9] Also, in comparison with normative data, a higher occurrence of sleep and behavioral problems is reported.[10] Although there is some knowledge about psychological adjustment of individuals with NF1, studies assessing QoL in children with NF1 are lacking.

The aim of this study was a comprehensive, standardized evaluation of QoL and psychological adjustment in children and adolescents with NF1 in comparison to healthy

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CBCL	Child Behavior Checklist	QoL	Quality of life
FRI	Family Relationship Index	TACQOL	TNO-AZL, Questionnaire for Children's Health-Related Quality of Life
NF1	Neurofibromatosis type 1		

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children. Based on clinical anecdotal evidence, we hypothesized that children and adolescents with NF1 would generally show a reduced health-related QoL as well as more psychological adjustment problems compared with healthy children.

METHODS

Subjects

Children and adolescents with NF1 meeting the diagnostic criteria of the National Institutes of Health Consensus Conference,[2] previously seen at the University Children's Hospital in Zurich or at the Children's Hospital in Aarau, and their parents were asked to participate in the study. For methodological reasons, the required age range at assessment was 7 to 16 years, and command of the German language was a prerequisite. Sixty-four children and adolescents met inclusion criteria. One patient with additional trisomy 21 was excluded from the study, and 17 patients refused to participate. The final sample comprised 46 participants (response rate, 72%).

Measures

TNO-AZL Child Quality of Life Questionnaire TACQOL[11]: The TACQOL is a generic instrument designed for QoL assessment in medical research and clinical trials. As a multidimensional instrument, it can be compared with questionnaires such as the PedsQL,[12] which is widely used for health-related QoL studies in children and adolescents in North America. The TACQOL is available in a child form (CF) and a parent form (PF), both containing five health status scales of eight items: physical complaints, basic motor functioning, autonomy, cognitive, social, positive emotional, and negative emotional functioning. Children and parents are asked to note problems in any of the mentioned domains and whether the child seems to be bothered by these problems. Maximum domain scores are 32 for the first five scales and 16 for the emotional scales. Higher scores represent a better QoL. Normal values for the child and parent forms are provided from a community sample of healthy Dutch children (child form: 1048 children/parent form: 1618 children).[11] Internal and external validity of the TACQOL has been confirmed in previous studies with healthy and clinical samples.[11]

Child Behavior Checklist CBCL[13,14]: The Child Behavior Checklist (CBCL) is a standardized measure with excellent psychometric properties providing parental reports of a child's behavior. It consists of 120 items assessing internalizing (social withdrawal, somatic complaints, anxiety/depression) and externalizing behavioral problems (dissocial and aggressive behavior). From these problem scales, an overall Total Behavioral Problems Score is calculated and compared with normative data (T-score). Reference values are provided by 2856 healthy German children and adolescents ages 4 to 18 years.[14]

Family Relationship Index FRI[15]: The FRI is a 27-item questionnaire consisting of three subscales of the Family Environment Scale, assessing expressiveness, cohesion, and conflict within a family. The FRI index is calculated as the sum of the subscales expressiveness and cohesion minus the subscale conflict. Higher scores indicated better family relationships. Reliability and validity of this scale have been confirmed.[15]

Illness-related variables: Illness-related variables such as family history of NF1 were obtained through review of the medical records for each child. The severity of NF1 was rated by using a modified version[6] of Riccardi's severity scale,[16] which has been widely used in previous studies.[5,6,8] The modified severity scale excludes cognitive features of NF1 and is based only on physical features. Four degrees of severity were distinguished: Minimal NF1 includes the presence of few features with no compromise of health or well-being. Mild NF1 means that there are enough features present to make the disease obvious and a source of concern, but without significant compromise of health. Moderate NF1 reflects the presence of significant compromise of health and well-being, though the compromise can be reasonably well managed. Severe NF1 indicates a serious compromise of health that is managed with difficulty, intractable, or associated with a shortened life span. The physical features of the modified severity scale were rated by the parents and confirmed with information from each child's medical record.

The visibility of NF1 was scored using a scale developed by Ablon[17] that has been used in previous studies.[5] Ratings are based on the appearance of a fully dressed person. Three different degrees of visibility were distinguished: Mild, moderate, and strong visibility. Ratings are based on cutaneous signs and features associated with gait and posture as well as ocular movements and orbital symmetry. Final scoring of severity and visibility was made by the first author, under the supervision of a neurologist with extensive experience in NF1.

Socioeconomic status: Socioeconomic status (SES) was calculated by means of a six-point scale of both paternal occupation and maternal education. The three social classes were defined as follows: SES scores 2 to 5, lower class; SES scores 6 to 8, middle class; and SES scores 9 to 12, upper class. This measure has been used in previous studies and has been shown to be a reliable and valid indicator of SES in our community.[18]

Procedure

The study was approved by the local research ethics committee. Parents were informed about the study by letter. Children and adolescents were assessed by means of a standardized interview. The interviews lasted between 30 and 60 minutes. Most interviews were conducted in the children's homes. Eight were done at the hospital. Parents were assessed at the same time point with questionnaires.

Statistical Analyses

Differences between the group of children and adolescents with NF1 and the reference sample groups were examined using Student *t*-tests. Spearman correlations were calculated to measure associations between both child QoL and psychological adjustment and various other variables. All analyses were performed with two-sided tests, and a value of $P < .05$ was considered significant.

RESULTS

Sample Characteristics

A total of 43 families with 46 affected children and adolescents participated in this study. Mean age at time of assessment was 11.6 years (range, 7.1 to 16 years). There were 33 boys (including four brothers) and 13 girls (none of them were sisters); sex was therefore not equally distributed ($\chi^2 = 8.7$, $P < .01$). Severity rating indicated that seven (15.2%) children had minimal NF1, 23 (50%) had mild, 12 (26.1%) had moderate, and four (8.7%) had severe NF1, including optic gliomas causing severe visual impairment (n = 2), tibial pseudoarthrosis (n = 1), and scoliosis requiring surgery (n = 1). The visibility of NF1 was distributed as follows: In 24 (52.2%) children, visibility was rated as mild, in 20 (43.5%) as moderate, and in two (4.3%) as severe. Severity and visibility of NF1 were not significantly correlated ($r = 0.13$, $P < .41$). The disease was familial in 18 (39.1%) children and sporadic in the remaining 28 (60.9%) children. Socioeconomic status could be calculated only for 44 children. The required data were missing for two families. The majority of families (31 of 44; 70.5%) were from the middle class, whereas seven (15.9%) and six (13.6%) were from the upper and lower classes, respectively. Participants of the study did not differ significantly from nonparticipants with regard to age, sex, and nationality. However, participants had a higher socioeconomic status than nonparticipants ($t = 2.57$, $P < .05$).

Quality of Life

Means and SD of the TACQOL scores are listed in Table I. Comparisons with the group of healthy children[11] show that the means of our sample patients were significantly lower in most dimensions of QoL, indicating an impaired health-related QoL in children with NF1. Children and parents both reported a significant impairment of motor, cognitive, social, and emotional functioning. Agreement between child and parent ratings was low to moderate (physical complaints: $r = 0.41$, $P < .01$; motor functioning: $r = 0.05$, $P = .74$; autonomy: $r = 0.13$, $P = .40$; cognitive functioning: $r = 0.41$, $P < .05$; social functioning: $r = 0.17$, $P = .26$; positive emotional functioning: $r = 0.35$, $P < .05$; negative emotional functioning: $r = 0.12$, $P = .43$).

Psychological Adjustment

Psychological adjustment as measured by the CBCL is reported in Table II. Compared with healthy children,[14] children with NF1 had significantly higher scores in all behavioral problem scales. Higher rates of internalizing behavioral problems indicate that children with NF1 are experiencing more social withdrawal, more anxiety and depressive symptoms, and more somatic complaints. Higher rates of externalizing behavioral problems refer to more aggressive and dissocial behavior. Analyses of T-scores revealed that about 39% of the sample patients had internalizing behavioral problems and about 24% had externalizing behavioral problems in the borderline/clinical range.

Table I. Sample means and normative data for quality-of-life measures (n = 46)

Measure	Sample Mean	Sample SD	Norms* Mean	Norms* SD	*P* value
TACQOL Child Form					
Physical complaints	25.2	4.2	25.0	5.1	.70
Motor functions	27.3	3.3	29.8	3.2	<.001
Autonomy	30.9	1.8	31.2	2.0	.19
Cognitive functions	24.3	4.3	28.5	4.0	<.001
Social functions	24.8	3.4	29.7	2.8	<.001
Positive emotions	12.2	2.5	13.6	2.5	<.001
Negative emotions	10.4	2.3	11.6	2.7	<.001
TACQOL Parent Form					
Physical complaints	26.5	4.1	27.2	3.9	.24
Motor functions	28.1	4.1	30.8	2.6	<.001
Autonomy	30.2	3.0	31.3	1.7	<.05
Cognitive functions	22.6	6.4	29.1	3.7	<.001
Social functions	26.9	4.9	29.9	2.5	<.001
Positive emotions	12.9	2.1	14.9	2.0	<.001
Negative emotions	10.8	2.5	11.5	2.4	<.05

*Normative data from manual scales (from Reference 11).

Table II. Sample means and normative data for psychological adjustment (n = 46)

Measure	Sample Mean	Sample SD	Norms* Mean	Norms* SD	*P* value
CBCL–Total†	58.3	9.8	50.0	10.0	<.001
CBCL–Internalizing†	58.1	9.6	50.0	10.0	<.001
CBCL–Externalizing†	54.3	10.4	50.0	10.0	<.01

*Normative data from manual scales (from Reference 14).
†T-scores.

Determinants of Quality of Life and Psychological Adjustment

No associations were found between sociodemographic variables and QoL or psychological adjustment (Table III). In contrast, some of the illness-related variables showed significant associations with QoL. Regarding the child self-report, both illness severity and visibility were significantly associated with an impaired QoL in the domain of positive emotions. Visibility was positively associated with higher QoL in the

Table III. Spearman correlation coefficients between TACQOL and CBCL scores and sociodemographic, illness-related, and family-related variables

Measure	Age	Sex	SES*	Severity	Visibility	Family history	FRI†	Cohes†	Expr†	Confl†
TACQOL Child Form										
Physical complaints	.15	.03	−.28	.07	−.05	−.37‡	.23	.20	.16	−.17
Motor functions	.13	−.26	−.23	−.13	−.04	−.10	.04	−.01	.13	.04
Autonomy	.20	−.20	−.22	−.06	−.25	.19	−.02	.05	.08	.08
Cognitive functions	−.17	.03	−.22	−.09	−.18	−.08	.18	.25	.16	−.01
Social functions	.02	−.08	−.06	−.04	−.26	−.03	.14	.18	.14	.01
Positive emotions	.02	−.20	.13	−.49§	−.44§	.04	.02	.03	.27	.26
Negative emotions	.11	−.23	−.07	.12	.34‡	−.19	−.04	−.02	−.05	.08
TACQOL Parent Form										
Physical complaints	.02	−.05	−.28	.27	.10	−.15	.32‡	.31‡	.12	−.38§
Motor functions	.21	.03	−.15	.01	−.17	.17	.05	.28	−.13	−.11
Autonomy	.34‡	.12	−.03	.17	−.06	−.04	.24	.22	.05	−.36‡
Cognitive functions	−.10	−.03	.03	.01	−.07	−.12	.28	.39§	.09	−.21
Social functions	.05	.08	−.11	.05	−.11	.13	.26	.38‡	.09	−.21
Positive emotions	−.08	−.03	−.01	−.39§	−.17	−.29‡	.20	.37‡	.20	.04
Negative emotions	.28	.06	−.08	−.01	.06	−.11	.09	.16	−.05	−.14
CBCL										
Total Scale	−.05	−.12	.14	.01	.03	.09	−.42§	−.36‡	.16	.49§
Internalizing Scale	−.02	−.19	.02	.00	.14	.12	−.34‡	−.42§	−.09	.40§
Externalizing Scale	−.12	−.07	.17	.05	−.04	.03	−.46§	−.27	−.24	.54§

*Socioeconomic status; † Family Relation Index (Cohes, Cohesion; Expr, Expressiveness; Confl, Conflict). ‡ $P < .05$, § $P < .01$.

domain of negative emotions. In sum, children with higher visibility experience less positive but also less negative emotions. In addition, familial NF1 was found to be significantly correlated with more physical complaints. Parental QoL report revealed a significant negative correlation between positive emotional functioning and familial NF1. However, psychological adjustment was not affected by illness-related variables.

Family-related variables were associated with some dimensions of parental reported QoL and psychological adjustment. High family cohesion positively affected most of the QoL domains. Also, high family cohesion and fewer conflicts had a significant positive impact on psychological adjustment, as measured by the three CBCL scores.

DISCUSSION

This cross-sectional analysis of health-related QoL and its determinants in children with NF1 used multiple informants. The results are consistent with our hypothesis, indicating that QoL of children and adolescents with NF1 is impaired and psychological adjustment is disturbed. Notably, compared with a healthy reference group, both children and parents reported a diminished child QoL in motor, cognitive, social, and emotional domains. Also, parents reported their children as showing higher rates of behavioral problems including both internalizing and externalizing behavioral problems compared with a community sample.

With regard to health-related QoL, our results are perfectly in line with those of Wolkenstein et al[5] in a population of adults with NF1. To our knowledge, however, no previous study has examined health-related QoL in children with NF1. Comparisons with studies in children with other chronic conditions clearly indicate that impairment in children with NF1 affects more QoL domains than in diseases such as phenylketonuria or nephrotic syndrome.[18,19] Notably, our finding of significant limitations across all relevant health dimensions in children with NF1 is consistent with previous results showing that chronic conditions involving the central nervous system are associated with more adjustment problems than non-neurologic chronic conditions.[20] Evaluation of agreement between child and parent ratings of QoL showed low to moderate correlations. Consistent with previous findings,[19,21] we found low agreement specifically in social and emotional domains. Not surprisingly, it seems difficult for a parent to gain insight into their child's social and emotional functioning, especially during adolescence.

Also, this study found higher rates of psychological maladjustment in children with NF1 compared with a community sample. In line with previous studies reporting an increased risk for emotional and social problems, our data also confirm higher rates of internalizing compared with externalizing behavioral problems in children with NF1.[7] Higher rates of internalizing behavioral problems may be explained by disease-specific neurocognitive problems, such as weariness, which may prevent children from acting out. In addition, methodological reasons must be considered: The CBCL-scale "Internalizing Behavioral Problems" contains the subscale "physical complaints." Thus, in chronically ill children, the occurrence of internalizing behavioral problems may be overestimated due to physical symptoms that are associated with the disease.[22] Higher rates of externalizing problems may

refer to elevated levels of attentional problems, which are consistently reported in children with NF1.[4]

This comprehensive investigation of children and adolescents with NF1 also identified several important determinants of QoL and psychological adjustment. Whereas sociodemographic variables were not significantly associated with QoL and psychological adjustment, illness- and family-related variables were important. Comparable with results in adults,[5] severity and visibility of the disease and the occurrence of familial NF1 were significant correlates of positive emotional and physical domains of QoL. The impact of familial NF1 on QoL is noteworthy, since 50% of NF1 is familial.[1] There are several possible explanations for this negative effect of familial NF1. Because of impairment in the parent's own QoL, there might be a shared variance between the parent's psychological strain and the rating of their child's QoL.[19] On the other hand, psychosocial impairment in parents can negatively affect adjustment in children.[23] Interestingly, none of the illness-related variables had a significant impact on psychological adjustment in this study. This contradicts previous studies reporting correlations between higher illness severity and deviant behavior.[24,25] One may speculate that NF1-related variables interfere with daily functioning, as measured by the QoL instruments, rather than causing significant psychological maladjustment. However, psychological adjustment was only rated by parents, not by the children themselves. Parents may be less aware of certain specific problems faced by their children, since they occur outside home.[21] Also, it may be possible that parental reports of problems in children may reflect parental beliefs about effects of the disease rather than actual states of the children.

With regard to family relationships, high family cohesion and fewer conflicts were positively related to parental reported child QoL and psychological adjustment. This finding is new for children with NF1. However, family characteristics have previously been identified as being crucial for positive adjustment in children with chronic conditions such as phenylketonuria, arthritis, and sickle cell disease as well as in healthy populations.[18,26,27] The pathways of family influence on the psychological development of children with chronic health conditions is not yet identified. Therefore, these findings deserve further study and may have practical relevance.

Strengths of this study include its use of children's self report and its multidimensional assessment of QoL. Nonetheless, some limitations of this study merit note. First, our sample is rather small, making statistically significant findings more difficult to achieve. Second, measuring psychological adjustment of children with NF1 using the general population as control subjects can be challenged, especially since the sensitivity of the CBCL regarding the detection of NF1-related consequences is undefined. A similar concern applies to the TACQOL. As a generic measure of health-related QoL, it is not specifically designed for children with NF1. However, at the time of this study, we were unable to find a disease-specific QoL questionnaire. Third, appropriateness of Dutch and German norms for our sample can be questioned. However, since the Netherlands, Germany, and Switzerland are neighboring central European countries with similar history as well as political, occupational, and familial structure, a major cross-cultural bias seems unlikely. Fourth, there may be limitations in the use of severity and visibility gradings. However, grading scales used by Riccardi[16] and Ablon[17] have been generally adopted and used in many studies. Finally, there may be some concerns regarding our correlational findings, since the chance of falsely significant results increases with more comparisons performed on the same set of data. Because this study had an exploratory character and the limited sample size did not allow multivariate analyses, subsequent studies are needed to confirm the findings.

This study suggests some possible issues for future research activities. This first application of the QoL concept to children and adolescents with NF1 may serve as a basis for future studies in other settings and countries. Furthermore, the development of a NF1-specific QoL measure must be considered. Finally, this study clearly demonstrates the importance of family-related variables. Future studies should therefore assess additional, possibly important predictors, such as parental adjustment.

Clinical implications can be drawn from this study. First, our findings confirm the need for careful evaluation of QoL and psychological adjustment in pediatric patients with NF1, because both domains may be seriously affected. Second, this study is an essential prerequisite for the development of interventions to improve the health-related QoL of children with NF1. Our results clearly show that the whole family must be considered to ameliorate the QoL and psychological adjustment in children and adolescents with NF1.

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