

Quality of Life in Children with Neurofibromatosis Type 1, Based on Their Mothers' Reports



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SUMMARY

Objective: The aim of this study was to investigate health-related quality of life (HRQoL) in children with neurofibromatosis type 1 (NF1) and to determine the factors affecting HRQoL in these children, with particular emphasis on NF1-specific findings and complications.

Materials and Methods: The patient group included 60 NF1 patients aged 3-18 years that were evaluated at our pediatric neurology outpatient clinic between January 2001 and January 2011. The control group included 96 age-matched patients without chronic disease and whose mothers had similar levels of education as the mothers of those in the patient group. All the mothers completed the Pediatric Quality of Life Inventory PedsQoL-Parent Form and the PedsQoL scores in the 2 groups were statistically compared. In addition, the effects of sociodemographic variables, as well as NF1-specific findings and complications (skin findings, neurofibromas, Lisch nodules, arterial hypertension and/or cardiac pathology, short stature, macrocephaly, orthopedic problems, hyperintense lesions on cranial MRI, epileptic seizures, psychiatric disease, and cognitive involvement) were statistically analyzed.

Results: All PedsQoL domain scores were lower in the patient group than in the control group ($P = 0.0001$). HRQoL decreased, and the number of NF1-specific findings and complications increased as age increased in the patient group ($P = 0.013$). Short stature, neurofibromas and/or plexiform neurofibromas, bone lesions, and psychiatric problems were factors specifically related to low-level HRQoL in the NF1 patients.

Conclusion: NF1 negatively affected HRQoL in the patient group. We think that multidisciplinary evaluation and, in particular, psychiatric management of NF1 patients are necessary to improve patient HRQoL.

Keywords: Neurofibromatosis type 1, quality of life, children

INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant neurocutaneous genetic disorder, with an incidence of 1 in 3000-4000 (Lammert et al. 2005; Poyhonen 2000; Gutmann et al. 1997); however, approximately 50% of cases develop as a result of a spontaneous mutation (North 1993). Findings in NF1 patients cannot be predicted and are quite variable and progressive. Furthermore, there may be marked variability within the same family. NF1 is a disorder that can affect the skin, the peripheral and central nervous system, and many other systems, including the skeletal, endocrine, gastrointestinal, and cardiovascular systems. Diagnosis of NF1 is based on the presence of ≥ 2 International Health Institute diagnostic criteria (Table 1) (NF 1988).

T2-weighted cranial MRI (cMRI) in NF1 patients shows an increase in density, starting with the early stages of the disease (Aoki et al. 1989). In such cases, the hyperintense lesions have distinct boundaries are thought to be hamartomas. The most common clinical findings in NF1 patients are cafe-au-

Table 1. NF1 diagnostic criteria

1. ≥ 6 cafe-au-lait spots measuring 5 mm in diameter before adolescence or ≥ 15 mm after adolescence).
2. ≥ 2 neurofibromas of the same type or 1 plexiform neurofibroma.
3. Axillary or inguinal freckling.
4. ≥ 2 Lisch nodules (iris hamartoma).
5. Optic nerve glioma.
6. Typical bone lesions (thinning or dysplasia with or without pseudoarthrosis of the long bones, sphenoid wing).
7. A first-degree relative with NF1, according to the above criteria.

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lait spots on the skin, cutaneous neurofibromas, freckling in skin folds, and Lisch nodules (iris hamartoma). In addition to esthetic problems in pediatric patients, more serious problems, including deformities due to plexiform neurofibromas (Packer and Rosser 2002), central nervous system tumors (optic glioma) (Gutmann et al. 2002), malignancies (malignant peripheral nerve sheath tumor, juvenile myelomonocytic leukemia, and rhabdomyosarcoma) (Matsui et al. 1993), endocrine disorders (early puberty and growth hormone deficiency) (Virdis et al. 2003), and orthopedic problems (scoliosis and skeletal dysplasias) are seen.

The most common complications of NF1 are behavioral problems and cognitive disorders. Mental retardation, language problems, learning disability, attention deficit-hyperactivity disorder (ADHD), autism, depression, and anxiety also frequently occur (Cnossen et al. 1998). There may also be relationship problems with friends due to poor social skills (Barton and North 2004; Johnson et al. 1999). When planning the management and treatment of NF1 patients, the negative effects on quality of life (QoL) due to the various physical, cognitive, and social complications should be taken into account.

QoL is defined as an individual's self perception of their status within their culture and value system (Spilker 1996). The concept of health-related QoL (HRQoL) increased in importance in the evaluation of healthcare data, clinical studies, and reports of new treatments during the second half of the 20th century (Eiser and Morse 2001). Currently, HRQoL scales are frequently used to understand the effects of a disorder on patients (Varni et al. 2005; Fidaner et al. 1999).

QoL scales for use with children and adolescents can generally be divided into 2 groups: those that were developed for a specific disorder and those that measure general wellbeing (Eiser and Morse 2001). A literature survey revealed that no QoL scale has been developed for NF1 patients. Studies based on scales developed for dermatological disorders and/or those that measure general wellbeing reported that QoL in adult NF1 patients was lower than in healthy individuals (Langenbruch 2011; Kodra 2009; Page 2006; Wolkenstein 2001). There are a limited number of and less comprehensive studies on NF1 in children and adolescents. Such studies examined the effects of such factors as behavioral problems, plexiform neurofibroma, orthopedic problems, learning disability, and the presence of psychological problems on QoL in children and adolescents with NF1 (Krab et al. 2009; Wolkenstein et al. 2009; Oostenbrink et al. 2007; Graf et al. 2006). As such, the aim of the present study was to identify the factors that negatively affect HRQoL in children with NF1, based on Pediatric Quality of Life Inventory (PedsQoL)-Parent Form scores, with an emphasis on NF1-specific findings and complications.

MATERIALS AND METHODS

The study included a patient group and control group.

Patient group

The charts of 112 pediatric patients diagnosed as NF1 that presented to Istanbul Medeniyet University, Göztepe Training and Research Hospital, Department of Pediatric Neurology, between January 2001 and January 2011 were evaluated according to the diagnostic measures shown in Table 1; 79 patients were selected to join the study. The families of these patients were contacted via telephone. In total, 65 patients aged 3-18 years and their mothers who agreed to participate in the study underwent a preliminary interview by a child psychiatrist. The patients' mothers were given information about the study during this interview, and were told how to complete the PedsQoL questionnaire and that their children would undergo psychometric testing. We excluded the children of 3 mothers that did not understand the study protocol or how to complete the questionnaire, as well as 2 children whose mothers did not agree to their psychometric evaluation.

In total, 60 pediatric NF1 patients that met the inclusion criteria were included in the study. Written informed consent was provided by the mother of each patient. Illiterate mothers received help completing the study forms from a relative. The children were reevaluated by a pediatric neurologist, and height, weight, head circumference, and arterial blood pressure were recorded. The obtained measurements were compared with healthy children percentile curves; patients below the 3rd percentile for height were diagnosed as short stature, those with blood pressure above the 97th percentile were diagnosed as hypertension, and those with a head circumference over +2 standard deviations were diagnosed as macrocephaly.

Findings recorded in the patient charts by the dermatology, ophthalmology, orthopedic, pediatric oncology, pediatric endocrinology, and pediatric cardiology specialists were evaluated according to our hospital's monitoring protocol; incomplete investigations were completed. The distribution of café-au-lait spots was evaluated, and a cosmetic problem was noted if there were spots on the face and/or the spots covered >30% of the body. Any axillary freckling, neurofibroma, or plexiform neurofibroma was also noted. During ophthalmic examination, the presence of Lisch nodules was noted. The presence of an optic nerve glioma, based on examination or orbital MRI, was also assessed. Bone lesions specific to NF1 diagnosed via direct X-ray were subsequently examined via computerized tomography (CT), and the findings were recorded. Any cardiology diagnoses based on electrocardiography and echocardiography findings were recorded. In terms of endocrinological evaluation, pubertal status (according to Tanner staging), short stature, and other findings were noted. Any malignant findings in a patient

or a family member with NF1 were recorded. Renal artery Doppler ultrasonography, abdominal ultrasonography, and cranial and spinal MRI findings were noted. The presence or absence of a NF1 Hyperintense Lesion (NHL) specific to NF1 based on cMRI was recorded. If a patient had a history of seizures, the International League Against Epilepsy (ILAE) epilepsy and febrile seizure classifications were used by a pediatric neurologist for diagnosis, based on clinical and electroencephalography (EEG) findings (Commission of ILAE 1989).

Psychiatric evaluation of the patients

A child psychiatrist interviewed the mothers and the patients. A semi-structured clinical interview was administered to the mothers to screen for symptoms of mental disorders according to DSM-IV diagnostic criteria. Children aged <7 years were evaluated in a free play environment and those aged ≥7 years were interviewed in accordance with the mental symptoms reported by their mothers. When necessary, a patient's teacher was sent an open-ended teacher information form and the reported data were evaluated.

The children's psychosocial development and intelligence were evaluated based on age-appropriate psychometric tests. The Denver Developmental Screening Test (DDST) II was used for children aged ≤6 years (Anlar and Yalaz 1996). Children with developmental delay for age according to the developmental stages were diagnosed as developmental retardation if consistent with the clinical evaluation. Children aged 6-16 years were administered the Wechsler Intelligence Scale for Children-Revised (WISC-R). Children with a total intelligence score <70 were diagnosed as mental retardation. Children with an intelligence score of 69-50 were diagnosed as mild mental retardation (Şavaşır and Şahin 1995). The same pediatric psychiatrist talked to the mothers about completing the questionnaires and the pediatric psychiatrist checked the forms after they were completed by the mothers.

Scales and psychometric tests in the patient group

Sociodemographic information form

A pediatric psychiatrist and a pediatric neurologist prepared a sociodemographic questionnaire to collect data on the mother's age and level of education, the child's birth history, and the family socioeconomic level. This form was completed by the physician, based on data obtained from the mother during the psychiatric interview and neurological examination.

Pediatric Quality of Life Inventory (PedsQoL)

PedsQoL is a general QoL questionnaire for children aged 2-18 years that is widely used to evaluate the physical and psychosocial status—independent of the disorder. The questionnaire was developed by Varni et al. (1999) and is highly valid

and reliable. The Turkish version of the scale was reported to be valid and reliable for use in Turkish children aged 2-7 years by Üneri et al. (2008) and in those aged 8-18 years by Memik et al. (2007). The Likert-type scale consists of 2 forms—a parent form for children and adolescents aged 2-18 years and a self-report form for children and adolescents aged 5-18 years. The scale can be completed in 5-10 min. The scale includes 4 subsections in which the level of physical, emotional, social, and school functioning is measured.

The physical functioning section includes 8 items, the emotional functioning section 5 items, and the social functioning section 5 items, while the school-related problems section had 3 and 5 items for the 2-4 years age group and other age groups respectively. Items were answered on a 5-point Likert-type scale (0: never; 1: rarely; 2: sometimes; 3: often; 4: always), whereas the form for the 5-7 years age group used a 3-point Likert-type answer scale (0: never; 2: sometimes; 4: always) to make it easier to understand.

Scores are linearly converted to a value between 0 and 100 (0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0). The scores of the 8 physical functioning domain items are directly converted and added, and then divided by 8 to obtain the physical function score. The psychosocial domain score is obtained by linearly converting the 5 emotional functioning items, the 5 social functioning items, and the 5 school functioning items, and then adding these and dividing by 15. The total score is obtained by linearly converting and adding all the scale's item scores and dividing by the total number of items (23). If <50% of the items are unanswered, the unanswered items are not considered and the score is calculated by dividing by the total number of items that were answered; if >50% of the items are unanswered the scale is not evaluated.

WISC-R

WISC-R was developed by Wechsler in 1949 and a revised form was developed in 1974 (Culbertson 1989). WISC-R consists of 2 sections: verbal and performance. The WISC-R-Turkish version was reported to be valid and reliable for use in Turkey by Şavaşır and Şahin (1995). The test provides verbal intelligence, performance intelligence, and total intelligence scores.

Denver Developmental Screening Test (DDST) II

The DDST II is a test used during a clinical interview to identify developmental problems and evaluate age-appropriate skills in children aged 0-6 years. The DDST II-Turkish Version was reported to be valid and reliable for use in Turkey by Anlar and Yalaz (1996). DDST II consists of 116 items in 4 domains: personal-social, fine motor, course motor, and language. It also includes 5 additional questions to evaluate how a child uses his/her abilities (Anlar and Yalaz 1996; Şavaşır and Şahin 1995).

Table 2. Sociodemographic features of the patient and control groups

Sociodemographic features	Patient Group n = 60	Control Group n = 96	P
Mean $\pm$ SD patient age (years)	10.2 $\pm$ 5.03	9.23 $\pm$ 3.65	0.165
Patient gender: Male, n (%)	24 (40)	45 (46.9)	0.400
Female, n (%)	36 (60)	51 (53.1)	
Mean $\pm$ SD age of the mothers (years)	36.45 $\pm$ 7.94	36.27 $\pm$ 5.58	0.284
Mothers' level of education			0.302
(can read and write), n (%)	6 (10)	10 (10.4)	
Primary-secondary school, n (%)	45(75)	79 (82.3)	
High school or above, n (%)	9 (15)	7 (7.3)	
Consanguinity, n (%)	16 (26.6)	-	
Presence of NF1 in the family, n (%)	30 (50%)	-	

n: Number of patients; SD: standard deviation; NF1: neurofibromatosis type 1

Control group

The control group included 96 children aged 3-18 years without a chronic health problem that were statistically matched with the study group for age, gender, and mother's age and level of education (Table 2).

The study was performed in 3 stages:

1. The PedsQoL scores in the patient and control groups were compared.
2. The relationship between PedsQoL scores and some sociodemographic features (maternal age and level of education, patient age and gender, the presence of NF1 in a family member) was evaluated to identify factors that may have had an effect on HRQoL in the NF1 patients. We also separated the NF1 patients according to whether the following findings or complications were present and compared PedsQoL scores between those with and without the following complications/findings: cosmetic problem, Lisch nodules, neurofibroma and/or plexiform neurofibroma, short stature, macrocephaly, epilepsy or febrile seizure, bone lesion, cardiovascular system diagnosis, NHL on cMRI, and psychiatric disorder.
3. The effect of a high number of NF1-specific findings and/or complications on HRQoL was investigated. We determined how many of the following systemic findings and diagnoses were present in each patient: skin findings, eye findings, dysmorphic findings (macrocephaly, short stature), psychiatric disorder, epilepsy and febrile seizures, orthopedic diagnosis, cardiovascular system diagnosis, endocrine system diagnosis, benign tumors, and malignancy. The number of findings and/or diagnoses listed above was referred to as the involvement number. We then investigated the correlation between the involvement number and mean PedsQoL scores in the patient group.

Statistical analysis

Statistical analysis was performed using NCSS 2007 software (Number Cruncher Statistical System, Utah, USA). Descriptive statistical methods (mean $\pm$ SD) were used for data evaluation, in addition to the following tests: one-way variance analysis (ANOVA) for intergroup comparisons; Tukey's multiple comparison test for subgroup comparisons; the independent t test for between-group comparisons; the chi-square test for comparison of qualitative data; Pearson's correlation test to determine the relationship between variables. The level of statistical significance was set at $P < 0.05$.

RESULTS

Patient and control group demographic data are shown in Table 2. Café-au-lait spots were observed in all patients (100%)—on the facial region in 15 (25%) and with dense distribution on the body in another 15 (25%). Axillary and/or inguinal freckling was noted in 27 patients (45%). A neurofibroma was present in 16 patients (26.6%), plexiform neurofibroma in 6 (10%) patients, Lisch nodules in 15 (25%) patients, optic glioma in 3 (5%) patients, short stature in 9 (15%) patients, macrocephaly in 15 (25%) patients, and a history of seizure (epilepsy or febrile seizure) in 9 (15%) patients. Based on orthopedic evaluation the following was observed in 16 (26.6%) of the patients: scoliosis (n = 5), curved tibia (n = 3), short tibia (n = 2), tibia pseudoarthrosis (n = 2), tibia solitary bone cyst (n = 1), tibia fracture (n = 1), fibula agenesis (n = 1), and clavicular dysplasia (n = 1)

Cardiac pathology was noted in 7 patients (11.6%) based on cardiologic evaluation, of which 6 had congenital heart disorders, including mitral valve prolapse, mitral regurgitation, aortic regurgitation, tricuspid and aortic valve regurgitation, and ebsteinoid valve, and of which 1 had left ventricular

Table 3. Distribution of NF1 patients, according to psychiatric diagnosis

Psychiatric Diagnoses	Patients (n)	%
Axis I Diagnoses	17	28.3
Anxiety Disorders	10	16.6
Sleep Disorder	4	6.6
ADHD	3	5
Phonological disorder	2	3.3
Depression	1	1.6
Enuresis	1	1.6
Autism	1	1.6
Mental or developmental retardation	11	18.3
Mental retardation (aged >6 years)	9	
Developmental retardation (aged ≤6 years)	2	
*Total number of diagnosed patients	25	41.6

*There may be more than one diagnosis in a patient.
ADHD: Attention deficit-hyperactivity disorder; NF1: neurofibromatosis type 1

Table 4. Mean ± SD PedsQoL scores in the NF1 patient and control groups

PedsQoL Scores	NF1 Patient Group n = 60	Control Group n = 96	P
Physical Health Total Score (PHTS)	67.9 ± 25.4	77 ± 16.7	0.008
Emotional Functioning Score (EFS)	69.7 ± 21.2	75.3 ± 15.3	0.048
Social Functioning Score (SOFS)	78.5 ± 20	86.4 ± 16.7	0.009
Psychosocial Health Total Score (PSHTS)	72.5 ± 18	81.7 ± 12.4	0.0001
School Functioning Score (SFS)	68.8 ± 24.5	87.6 ± 11.3	0.0001
Scale Total Score (STS)	70.7 ± 17.2	80.1 ± 12.3	0.0001

QoL: Quality of life; n: number of patients; SD: standard deviation; NF1: neurofibromatosis type 1

Table 5. The effect of patient age, and mother's age and level of education on PedsQoL scores in the NF1 patient group

Sociodemographic factors		PHTS	EFS	SOFS	PSTS	SFS	STS
Patient Age	r	-0.195	-0.142	-0.035	-0.104	-0.144	-0.199
(years)	P	0.015	0.078	0.665	0.204	0.108	0.013
Mother's Age	r	-0.126	0.061	0.012	0.033	-0.053	-0.05
(years)	P	0.118	0.453	0.885	0.682	0.556	0.537
Mother's Education	P	0.154	0.075	0.088	0.074	0.377	0.018
Can read and write							
mean± SD		58.3 ± 24.1	54.1 ± 27.4	67.5 ± 17.8	59.5 ± 16	56.8 ± 30.7	58.6 ± 18.0
Primary Education							
mean± SD		66.4 ± 25.9	69.9 ± 20.7	77.7 ± 20.9	72.9 ± 18.4	69.8 ± 24.1	69.8 ± 17.0
High School and Above							
mean± SD		81.9 ± 19.8	79.4 ± 13.3	90 ± 11.1	82.9 ± 7.41	77.5 ± 14.43	83.2 ± 10.4

QoL: Quality of life; SD: standard deviation; NF1: neurofibromatosis type 1; PHTS: physical health total score; EFS: emotional functioning score; SOFC: social functioning score; SFC: school functioning score; PSTS: psychosocial health total score; STS: scale total score.

hypertrophy. Renal artery stenosis was noted in two patients (3.3%) as a vascular complication of NF1, and the number of NF1 patients with cardiovascular involvement was 9. Four (6.6%) patients also suffered from hypertension. Four (6.6%) patients had an endocrine system diagnosis (early puberty [n = 2] and growth hormone deficiency [n = 2]), whereas 33 (56.8%) of the 58 patients that underwent cMRI had NHL in various regions.

Psychiatric evaluation indicated that 25 patients (41.6%) had a psychiatric disorder based on DSM-IV diagnostic classification. In all, 17 patients had an Axis I diagnosis (28, 3%), and 11 patients (18, 3%) had mental retardation or developmental retardation (some patients had more than one diagnosis).

The distribution of psychiatric disorders is shown in Table 3. Table 4 presents the mean PedsQoL scores in the NF1 patient and control groups, together with statistical comparison of the 2 groups. All PedsQoL domain scores were significantly lower in the NF1 patients. There was a strong negative relationship between age and PedsQoL total score; as age increased HRQoL decreased, which was due solely to physical functioning. There was no relationship between maternal age and PedsQoL scores (Table 5). Then the mothers were divided into three groups depending on their educational level (has not attended school but knows how to read and write, primary school graduate, high school graduate or above) and analyzed accordingly, we found that the mother's educational level had a positive effect on the patient's total quality of life

Table 6. NF1-specific findings that affected HRQoL in the NF1 patients and mean PedsQoL scores in the patients with such findings

NF1-Specific Finding	PHTS	EFS	SOFS	PSTS	SFS	STS
Short Stature	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)
Present (n = 9)	64.1 $\pm$ 22	47.2 $\pm$ 25.9	59.4 $\pm$ 22	53.8 $\pm$ 21.8	55 $\pm$ 31.4	56.7 $\pm$ 20.9
Absent (n = 51)	68.6 $\pm$ 26.1	73.7 $\pm$ 17.7	81.9 $\pm$ 17.8	76.1 $\pm$ 14.9	72.2 $\pm$ 21.6	73.2 $\pm$ 15.5
P	0.631	0.0001	0.001	0.0001	0.048	0.007
Bone Lesion	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)
Present (n = 16)	74.3 $\pm$ 23.3	72.7 $\pm$ 20.8	81.1 $\pm$ 20.4	74.5 $\pm$ 18.4	69 $\pm$ 23.9	74.5 $\pm$ 16.8
Absent (n = 44)	50.2 $\pm$ 22.8	61.5 $\pm$ 20.5	71.5 $\pm$ 17.7	67.5 $\pm$ 16.3	68 $\pm$ 26.7	60.3 $\pm$ 14.3
P	0.001	0.071	0.103	0.191	0.901	0.004
Neurofibrom/Plex.	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)
Neurofibrom						
Present (n = 18)	49.9 $\pm$ 22.4	57.8 $\pm$ 20.3	72.5 $\pm$ 18	65 $\pm$ 19.5	64.7 $\pm$ 28.3	58.8 $\pm$ 13.8
Absent (n = 42)	75.6 $\pm$ 22.7	74.8 $\pm$ 19.6	81.1 $\pm$ 20.5	76.1 $\pm$ 16.3	71.5 $\pm$ 21.7	75.8 $\pm$ 16.1
P	0.0001	0.003	0.125	0.03	0.368	0.0001
Psychiatric Disorder	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)
Present (n = 25)	57.6 $\pm$ 24.4	58.6 $\pm$ 22.2	69.0 $\pm$ 19.8	62.6 $\pm$ 18.8	60.2 $\pm$ 28.2	60.6 $\pm$ 15.2
Absent (n = 35)	75.3 $\pm$ 23.8	77.7 $\pm$ 16.6	85.4 $\pm$ 17.4	80.5 $\pm$ 12.8	77.7 $\pm$ 16.0	78.0 $\pm$ 14.9
P	0.007	0.0001	0.001	0.0001	0.015	0.0001
Axis I Diagnosis	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)
Present (n = 17)	55.4 $\pm$ 24.7	57.6 $\pm$ 22.1	73.5 $\pm$ 18.6	65.9 $\pm$ 16.7	67.3 $\pm$ 26.1	61.8 $\pm$ 13.7
Absent (n = 43.8)	72.8 $\pm$ 24.2	74.5 $\pm$ 19.0	80.5 $\pm$ 20.4	75.4 $\pm$ 17.9	69.5 $\pm$ 24.0	74.3 $\pm$ 17.4
P	0.016	0.004	0.22	0.069	0.78	0.01
Mental/Development.	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)	(mean $\pm$ SD)
Retardation						
Present (n = 11)	62.7 $\pm$ 25.1	53.6 $\pm$ 26.2	60.9 $\pm$ 21.6	53.03 $\pm$ 21.9	44.5 $\pm$ 30.9	56.5 $\pm$ 21.5
Absent (n = 49)	69.1 $\pm$ 25.6	73.3 $\pm$ 18.3	82.5 $\pm$ 17.5	77.3 $\pm$ 13.3	75.7 $\pm$ 17.3	73.9 $\pm$ 14.6
P	0.455	0.004	0.001	0.0001	0.0001	0.002

QoL: Quality of life; n: number of patients; SD: standard deviation; T.S.: total score; NF1: neurofibromatosis type 1; Plex: Plexiform; PHTS: physical health total score; EFS: emotional functioning score; SOFC: social functioning score; SFC: school functioning score; PSTS: psychosocial health total score; STS: scale total score

score (table 5). The Tukey multiple comparison test was used to evaluate which differences between the groups regarding the mothers' educational level caused this effect. We found that the mean total quality of life score of children whose mothers had not attended school but could read and write were significantly lower than the children of mothers who were high school graduates or above ($P = 0.017$).

We did not find a statistically significant effect of gender or the presence of another NF1 patient in the family on the quality of life scores ($P > 0.05$).

Dense distribution of café-au-lait spots on the body, and the presence of axillary and/or inguinal freckling had no effect on PedsQoL scores ($P > 0.05$). Mean PedsQoL scores in the

patients with neurofibroma and/or plexiform neurofibroma were significantly lower than in those without neurofibroma or plexiform neurofibroma. This difference was primarily due to the physical and emotional functioning scores, and to a smaller degree the psychosocial functioning score. Mean PedsQoL total score in the patients with short stature was significantly lower than in those with normal height. The presence of a bone lesion was associated with significantly lower PedsQoL physical functioning score (Table 6); however, there was no significant difference regarding PedsQoL scores between NF1 patients with and without a Lisch nodule, between NF1 patients with macrocephaly and normal head circumference, between NF1 patients with and without a history of epilepsy/febrile seizure, between NF1 patients

Table 7. Correlation between involvement number and PedsQoL scores in the NF1 patient group

		PHTS	EFS	SOFS	PSTS	SFS	STS
Involvement	r	−0.444	−0.408	−0.282	−0.316	−0.029	−0.468
number	P	0.0001	0.001	0.029	0.018	0,852	0.0001

NF1: Neurofibromatosis type 1; PHTS: physical health total score; EFS: emotional functioning score; SOFC: social functioning score; SFC: school functioning score; PSTS: psychosocial health total score; STS: scale total score

with and without cardiovascular pathology, or between NF1 patients with and without NHL ($P > 0.05$).

In total, 25 (41.6%) of the patients had an Axis I disorder and/or mental retardation/developmental retardation. Among the 10 patients diagnosed as anxiety disorder, 1 also had a sleep disorder, 1 also had a phonological disorder, and 1 also had depression. Phonological disorder as the sole disorder was observed in 1 patient. ADHD was diagnosed in 3 patients, and 1 was diagnosed with enuresis and autism. Sleep disorder was observed in 2 patients, 2 had developmental retardation (aged ≤ 6 years), and 9 patients had mental retardation (aged ≥ 6 years). All patients with mental retardation had mild severity. Mean PedsQoL scores were significantly lower for all domains in the patients with ≥ 1 psychiatric disorder (Axis I and/or mental retardation/developmental retardation) than in the patients without such a disorder. All PedsQoL domain scores, except physical functioning, were significantly lower in the patients with mental and developmental retardation than in those without the disorders. Patients with an Axis I disorder also had significantly lower PedsQoL physical and emotional functioning scores, and total score than those without an Axis I diagnosis (Table 6).

Evaluation of the relationship between the number of findings and diagnoses specific to the NF1 disorder and the quality of life scores revealed a statistically significant negative correlation between the involvement number and the physical functioning score, emotional functioning score, social functioning score, psychosocial functioning score, and the total score. We found no correlation with the school functioning score (table 7).

DISCUSSION

The present findings show that NF1 had a negative effect on the PedsQoL physical, emotional, social, psychosocial, and school domain scores. As the number of NF1-specific findings increased, patient HRQoL decreased. Graf et al. (2006) conducted the first large-scale study on HRQoL in children and adolescents with NF1, evaluating 46 children and adolescents aged 7–16 years, and reported low-level HrQoL in the patients. Another study that included 34 children aged 12–72 months observed that NF1 had a negative effect on HRQoL, according to parental reports (Oostenbrink et al. 2007). Two other studies based on parental reports evaluated 58 and 79

children with NF1 and reported similar results (Krab et al. 2009; Wolkenstein et al. 2009). In the present study PedsQoL was completed by mothers and as previously reported showed that NF1 had a negative effect on HRQoL in the 60 pediatric and adolescent patients included.

In the present study, HRQoL decreased as patient age increased. Krab et al. (2009) also reported a similar age-HRQoL relationship in patients with NF1. These findings are likely due to the emergence of many complications—especially dermatological—during the late stage of the disease. Some HRQoL studies have reported that the family income decreases with decreasing educational level of the parents and that it is difficult for parents with a low educational level to meet their children's needs and that the quality of life of the children may therefore be affected by the low educational level of the parents (Oostenbrink et al. 2007). The fact that we found educational level to be one of the factors influencing quality of life also supports this notion.

The effect of gender on the quality of life is controversial (Eiser 2001). Some studies report no effect on gender on the quality of life in NF1 patients (Graf et al. 2006, Wolkenstein et al. 2009). Our study findings also support the lack of an effect of patient gender on the quality of life.

Fifty percent of the present study's patients had familial NF1. Some studies report that familial NF1 may positively affect disease prognosis and that family members provide social support to affected children (Krab et al. 2009; Oostenbrink et al. 2007; Graf et al. 2006); however, in the present study familial NF1 had no effect on HRQoL. The differences in findings may be due to differences in cultural characteristics of the study populations, but other studies that investigate the effects of familial NF1 on HRQoL are needed.

Studies on adult NF-1 patients have found a markedly negative effect of the quality of life in patients with severe findings according to scales that evaluate the disorder-specific findings. Similar results have been reported for the pediatric and adolescent group (Wolkenstein et al. 2009, Graf et al. 2006, Oostenbrink et al. 2007, Krab et al. 2009). We did not use a grading scale regarding NF1 findings and complications in our study. We evaluated each finding and complication separately, assessed the affect on the quality of life, and individually discussed the findings and complications with a potential effect, in contrast to other studies. NF1 findings change with

age. Some findings may not appear in the early ages and some findings and complications can become more prominent during adolescence and even during adulthood.

It was reported that evaluating the visibility and severity of the disorder in adult patients provides a more informative and reliable evaluation than those in children (Krab et al. 2009), which is especially valid for dermatological findings. Studies using the Ablon visibility scale in adult patients report that HRQoL is markedly negatively affected by cosmetic findings (Wolkenstein et al. 2001; Ablon 1996). Using a similar method, a study on pediatric NF1 patients reported that the effect of cosmetic problems specific to NF1 on HRQoL was lower than the effect of severe dermatological problems, such as psoriasis, eczema, and acne, but greater than the effect of subnormal conditions, such as a nevus (Wolkenstein et al. 2009). A study that included NF1 patients aged 12-72 months that was based on the ITQoL (Infant Toddler Quality of Life) scale reported that moderate visibility had no effect on QoL (Oostenbrink et al. 2007); however, some studies used Skindex to evaluate skin findings in adult patients (Kodra et al. 2009; Page et al. 2006) and the CDLQI (Children's Dermatology Life Quality Index) to evaluate skin findings in children (Wolkenstein et al. 2009). In the present study the presence of café-au-lait spots on the face, dense distribution on the body, and axillary/inguinal freckling that could create a cosmetic problem did not bother the mothers regarding physical, emotional, or social functioning, based on the PedsQoL (not a dermatology-specific questionnaire prepared for children), and as such the findings may not be definitive; most of the patients were in the childhood age group in which dermatological complications were not important. Wolkenstein et al. (2009) reported that café-au-lait spots and axillary freckling are not important factors for HRQoL in children. Neurofibromas and plexiform neurofibromas are reported to affect QoL because of their appearance, and the associated pain and discomfort (Wolkenstein 2009). In the present study neurofibromas and/or plexiform neurofibromas had a negative effect—in general—on PedsQoL emotional, physical, and psychosocial functioning domain scores.

Orthopedic findings are another physical cause of decreased HRQoL. Wolkenstein et al. (2009) evaluated 79 children with NF1 and HRQoL in 29 (33%) of the cases that had an orthopedic problem was lower than in those with other chronic disorders. In the present study, PedsQoL physical functioning and total scores were lower in the patients that had orthopedic findings, including scoliosis, short long bones, agenesis, fracture, curvature of bones, and pseudoarthrosis, which is an expected finding. A literature review showed that short stature occurs in 13% of NF1 patients, but had not been studied regarding its effect on QoL (Szudek et al. 2000). Short stature was observed in 15% of the present study's NF1 patients, of which all had lower PedsQoL domain scores, except

for physical functioning, than the NF1 patients with normal height. New studies with larger series are needed to comment on relationship between HRQoL and short stature.

Other NF1-specific findings, such as Lisch nodules, NHL based on cMRI, and the presence of macrocephaly did not have a significant effect on HRQoL in the present study. Lisch nodules and NHL based on cMRI are hamartomatous lesions not associated with additional complications, which may be why they did not have a negative effect on HRQoL. HRQoL was lower in the patients with cardiovascular system pathology, and epilepsy or febrile seizure, but not significantly, perhaps due to the small number of patients with seizure or cardiovascular findings.

NF1 patients are reported to frequently suffer from memory problems, learning disability, mental retardation, language problems, and cognitive disorders, including ADHD (Krab et al. 2009; Hyman et al. 2005; Ozonoff 1999). These children also frequently experience shyness, anxiety disorders, depression, and aggressive behavior (Krab et al. 2009; Graf et al. 2006; Descheemaeker et al. 2005; Johnson et al. 1999). In the present study, a comorbid psychiatric diagnosis had a negative effect on HRQoL. All PedsQoL domain scores, except physical functioning, were lower in the NF1 patients with mental and developmental retardation, whereas an Axis I diagnosis was associated with lower PedsQoL physical functioning, emotional functioning, and total scores. Our results highlight the importance of psychiatric evaluation in NF1 patients. Evaluation and treatment of any additional psychiatric problems seems important during the follow-up and in increasing the quality of life of NF1 patients. Following the intelligence level may make it possible to increase the children's quality of life by enabling the determination of children where mental retardation and ADHD may affect academic success so that they can be directed to special educational support and the family can be made aware of the problem.

There are no valid and reliable QoL scales specifically designed for children with NF1, which may have prevented us from determining some of the factors that affected HRQoL in the present study's NF1 patients. NF1-specific HRQoL scales are needed in order to obtain more reliable findings concerning the factors that affect HRQoL in NF1 patients. The present study included preschool-aged children and therefore we used the PedsQoL -Parent Form. A limitation of the study is that the PedsQoL questionnaire was completed by the patients' mothers. To the best of our knowledge, the present study is the first to evaluate HRQoL in Turkish children with NF1.

In conclusion, HRQoL decreased in the NF1 patients as age, and the number of NF1-specific findings and complications increased. In addition to short stature, bone lesions, and fibromas and/or plexiform neurofibromas were other factors that negatively affected HRQoL, as did the presence of a

psychiatric disorder, and mental and developmental retardation. It is therefore important to request psychiatric consultation during the follow-up of pediatric NF1 patients and to assemble a multidisciplinary treatment team in order to improve their HRQoL.

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