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Evaluation of quality of life and its associations with clinical parameters in pediatric patients with familial Mediterranean fever

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ABSTRACT

OBJECTIVE: A favorable quality of life (QoL) is important in children with chronic disease, and it reflects successful disease management. The aim of our study was to evaluate QoL and its association with clinical parameters in pediatric patients with familial Mediterranean fever (FMF).

METHODS: The Kinder Lebensqualität Fragebogen (KINDL®) questionnaires (kiddy: 4–7 years; kid: 8–16 years) for children and the proxy version for parents were implemented as a QoL measure. A total of 171 FMF patients, 69 healthy peers and their parents were enrolled in the study.

RESULTS: The KINDL QoL scores of the FMF patients were significantly lower than their healthy peers. The physical and emotional well-being KINDL QoL scores of the FMF children were significantly lower than their healthy peers (p=0.017 and p=0.020, respectively). In the evaluation of the KINDL QoL scores between the kiddy and kid groups, only the self-esteem score was higher in the kiddy group (p=0.004), and the school functioning scores were higher in the kid group (p=0.002). The scores in the physical well-being and disease module had significant differences between patients who were adherent and those who were non-adherent to colchicine therapy (p=0.042 and p=0.047, respectively). The scores in the physical well-being and disease module were significantly higher in patients with fewer attacks than those who had many attacks per year (p=0.004 and p=0.014, respectively).

CONCLUSION: This study suggests that FMF patients have significantly impaired QoL. The irregular use of colchicine and more frequent attacks affect QoL even more. A QoL assessment with multidisciplinary follow-up and control of the disease activity are essential, and if necessary, individualized support should be given to patients.

Keywords: Familial Mediterranean fever; pediatric rheumatology; quality of life.

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Familial Mediterranean fever (FMF) is the most common autosomal recessive inherited autoinflammatory disorder. It is characterized by recurrent fever attacks with peritonitis, pleuritis, and pericarditis. FMF attacks are typically self-limited and usually resolve within 12–72 h. FMF patients with poor disease control can develop chronic complications such as amyloidosis and chronic arthritis [1]. Colchicine, an inexpensive and well-toler-

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ated treatment for FMF, reduces attacks and prevents the development of amyloidosis in most patients [2]. In recent years, anti-interleukin-1 (IL-1) treatments have shown additional benefits in those resistant to colchicine therapy [3].

Chronic disease can affect patients' quality of life (QoL) due to changing lifestyles throughout the course of the disease. A favorable QoL is important in children with chronic disease in terms of managing the disease, determining disease prognosis, and preventing chronic complications from the disease. FMF has a substantial impact on daily activities, schooling and family functioning in children [4]. In particular, FMF patients who have a severe disease course and/or amyloidosis have a reduced QoL [4, 5].

The aim of our study was to evaluate QoL and its association with clinical parameters in pediatric patients with FMF. QoL comparisons with healthy controls were also performed.

Highlight key points

- FMF had a negative impact on quality of life in patients, such as physical well-being, emotional well-being, and school functioning.
- The irregular use of colchicine and more frequent attacks affect quality of life detrimentally.
- Assessing quality of life with multidisciplinary follow-up and controlling disease activity are essential for management of FMF.

MATERIALS AND METHODS

A cohort of 171 children diagnosed with FMF was enrolled in the study. The control group consisted of 69 age- and gender-matched healthy controls. All of the FMF patients were aged 4–16 years old and had the illness for 6 months or more; patients undergoing treatment at Gazi University Pediatric Rheumatology Department between June 2018 and June 2019 were asked to participate in this study. The healthy controls, children who visited the general pediatric outpatient clinics for either vaccinations or general check-ups, were invited and volunteered to participate in the study. FMF patients who had an additional chronic disease were excluded from the study. All FMF patients were evaluated clinically according to the Tel Hashomer criteria [6]. Demographic data, clinical manifestations, number of attacks in previous year, number of emergency room visits, treatment responses, disease complications, family history, compliance with treatment, laboratory features, and Mediterranean fever gene mutations were recorded for each patient. All of the patients were in an attack-free period while they were enrolled in the study. All patients were receiving colchicine treatment. The biologics targeting IL-1 were started with these FMF patients due to inadequate response, non-compliance or intolerance to colchicine, or the development of secondary amyloidosis. Partial response to colchicine therapy was accepted as a decrease in attack frequency while colchicine resistance was accepted in cases where all FMF symptoms were not resolved or acute-phase reactants did not decrease [5]. The Pras activity score was used to evaluate disease severity in FMF patients [7]. Patients who had been undergoing colchicine therapy for at least 6 months were included in the study. All patients and healthy volunteers were evaluated by a pediatric rheumatology doctor, a social worker, and a psychologist.

QoL Evaluation

The Turkish version of the Kinder Lebensqualität Fragebogen (KINDL®) questionnaires (kiddy: 4–7 years; kid: 8–16 years) for children and the proxy version for parents were implemented as a QoL measure [8]. The self-reported form for ages 4–7 comprises 12 items with three categorical answers. The other form for ages 8–16 consists of 24 items equally distributed into six subscales: physical well-being (e.g., felt sick), emotional well-being (e.g., felt fearful or insecure), self-esteem (e.g., was happy with myself), well-being related to family (e.g., felt comfortable at home), well-being related to friends/peers (e.g., got along with friends), school-related well-being (e.g., was afraid of getting bad grades), and a disease perception subscale for chronic conditions (e.g., being afraid that my illness might get worse; being sad because of my illness; being unable to cope well with my illness; being afraid of others noticing my illness; and being afraid of missing something at school because of my illness). Each item addresses experiences over the previous week and is rated on a 5-point scale (1=never, 2=seldom, 3=sometimes, 4=often, and 5=always). Mean scores are calculated for each of the six subscales and for the total scale and then linearly transformed to a 0–100 scale. Higher scores indicate better QoL. Details about the questions can be found on the KINDL web site (www.kindl.org). Differences in these domains were compared between the FMF patients and the healthy controls.

Statistical Analysis

Statistical analysis of the data was performed by Statistical Package for the Social Sciences (SPSS) software version 15 (SPSS Inc., Chicago, IL, USA). Variables are presented as mean±standard deviation or median (minimum–maximum) according to the distribution of the data. Normality of the distribution of continuous variables was determined using Kolmogorov–Smirnov test. The differences between two independent groups were compared using independent sample t-test for normally distributed variables or Mann–Whitney U-test for non-normally distributed ones. The differences between three independent groups were compared using one-way ANOVA with Tukey post hoc test for normal distributions or Kruskal–Wallis test with Bonferroni correction for non-normal distributions. $P<0.05$ was considered to be statistically significant. This study was approved by the Gazi University Faculty of Medicine Ethics Board (June 11, 2018/456) and was conducted in accordance of the Declaration of Helsinki. Informed consents were obtained from each participant's caregivers.

RESULTS

A total of 171 patients (75 males and 96 females) with FMF and 69 healthy controls (30 males and 39 females) were included in the study. The mean ages of the patients and healthy controls were 11.6±3.7 and 11.3±3.9 years old, respectively. No significant differences in age and gender were found between the patients and healthy controls. Of the FMF patients, 30 (17.5%) were non-compliant with daily colchicine therapy. The clinical and genetic characteristics of the patients are given in Table 1.

The KINDL QoL scores of the FMF children were significantly lower than those of the healthy controls for general and school functioning on the child self-report and parent proxy-report (Table 2). In addition, the physical and emotional well-being KINDL QoL scores of the FMF children were significantly lower than those of their healthy peers ($p=0.017$ and $p=0.020$, respectively). There were no significant differences in the KINDL QoL scores for self-esteem, family, and friends on either the child self-report or parent proxy-report.

The relationship between the KINDL QoL scores and the clinical features of the patients is summarized in Table 3. There were no significant differences between males and females in any domains of the KINDL QoL scores of the FMF patients. In the evaluation of

Table 1. Demographic features of FMF patients

Variable	%
FMF symptoms	
Abdominal pain	88.9
Fever	99.4
Arthritis	38.6
Chest pain	24
Erysipelas-like erythema	16.4
Attack frequency (attack per year)	
<1	42.1
1–2	38.6
>2	19.3
Emergency visits frequency in a year (visit per year)	
<1	57.3
1–2	34.5
>2	8.2
Median of Pras score (median 6)	
Mild course	31.6
Moderate course	50.3
Severe course	18.1
Compliance of colchicine treatment	
Adherent	82.5
Non-adherent	17.5
Response of colchicine treatment	
Complete	88.9
Partial	7
Resistant	4.1
Anti-IL-1 treatment	9.4
MEFV mutation	
Homozygous	
M694V/M694V	28.7
M680I/M680I	3.5
V726A/V726A	1.2
E148Q/E148Q	0.6
Compound heterozygous	
M694V/M680I	7
M694V/V726A	6.5
M694V/E148Q	3.5
M680I/V726A	2.9
M694V/R761H	2.3
V726A/E148Q	2.3
M694V/P369S	1.2
Heterozygous	
M694V	18.1
M680I	7
V726A	4.7
E148Q	2.3
P369S	2.3
No mutation	5.8

FMF: Familial Mediterranean fever; MEFV: Mediterranean fever; anti-IL-1: Anti-interleukin-1.

Table 2. Parent proxy-reported and child self-reported KINDL QoL scores of pediatric patients with FMF and healthy children

Scale	FMF patients (n=171)		Healthy controls (n=69)		p
	Mean	SD	Mean	SD	
Children (4–16 years)					
Self-report					
General	71.3	11.9	75.2	10.0	**0.013**
Physical well-being	65.0	23.3	72.9	19.8	**0.017**
Emotional well-being	74.2	17.5	79.2	12.8	**0.020**
Self-esteem	69.8	20.6	72.0	20.4	0.458
Family	77.2	16.1	79.3	19.4	0.402
Friends	72.2	16.0	72.6	14.7	0.852
School functioning	69.2	18.4	74.9	19.7	**0.039**
Parent proxy-report					
General	69.2	12.3	72.8	12.3	**0.046**
Physical well-being	64.9	23.5	69.4	21.4	0.182
Emotional well-being	73.2	17.8	71.0	18.9	0.415
Self-esteem	62.6	25.5	66.1	21.1	0.337
Family	82.6	16.5	84.7	16.2	0.383
Friends	77.7	18.0	77.6	20.3	0.964
School functioning	54.0	26.5	68.6	20.6	<**0.001**

KINDL: Kinder Lebensqualität Fragebogen; FMF: Familial Mediterranean fever; SD: Standard deviation.

the KINDL QoL scores between the kid and kiddy groups, only the self-esteem score was higher in the kiddy group than in the kid group (p=0.004), and school functioning scores were higher in the kid group than in the kiddy group (p=0.002). The scores in the physical wellbeing and disease module showed significant differences between patients who were adherent and those who were non-adherent to colchicine therapy (p=0.042 and p=0.047, respectively). The scores in the physical well-being and disease module were significantly higher in patients with fewer attacks than those who had many attacks per year (p=0.004 and p=0.014, respectively).

DISCUSSION

Awareness of deficiencies in QoL in rheumatic diseases is important for disease management due to the course of these chronic diseases. We demonstrated that FMF had a negative impact on QoL in patients in comparison to healthy peers, particularly on physical well-being, emotional well-being, and school functioning. However, the scores in the self-esteem, friends, and family domains in the FMF patients were similar to those in the healthy controls. In the previous studies, impaired QoL has been reported for both children and adults with FMF [4, 9, 10].

In 2009, Makay et al. [4] reported lower scores in all QoL domains in pediatric FMF patients. In addition, in 2014, Alayli et al. [11] described similar findings. In our study, unlike these other studies, we found low QoL scores in some domains (physical well-being, emotional well-being, and school functioning) rather than all domains of QoL. School functioning was the most affected domain in the KINDL QoL scores, which shows that missing school because of routine hospital visits and unplanned emergency room visits due to FMF attacks affected the patients' feelings about school. In recent years, anti-IL-1 therapy has become widespread across the world. People are also able to easily access detailed information about FMF, including new treatment options, on the internet. In addition, there has been an increase in the number of pediatric rheumatology centers in our country during the past 10 years. All of these may be reasons for the improvement in the QoL of FMF patients, compared to the previous studies. Varan et al. [12] also described a sig-

TABLE 3. Relationship between KINDL QoL scores and clinical features of patients

Parameter	Status	General		PW		EW		SE		FA		FR		SC		CG	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Gender	Male (n=75)	68.9	13.2	65.2	23.0	72.5	18.7	61.9	27.2	79.8	17.8	80.2	16.3	53.8	26.0	62.8	21.9
	Female (n=96)	69.4	11.6	64.7	24.0	73.8	17.0	63.2	24.3	84.8	15.3	75.8	19.1	54.1	27.0	58.4	23.2
	P-value	0.802		0.901		0.646		0.755		0.053		0.114		0.948		0.203	
Age	Kiddy (n=38)	68.1	13.7	61.8	27.7	68.4	23.7	73.0	24.9	84.9	21.4	78.3	23.4	42.1	46.5	53.5	21.9
	Kid (n=133)	69.5	11.9	65.8	22.2	74.6	15.5	59.6	25.0	82.0	14.9	77.5	16.2	57.4	15.6	62.3	22.6
	P-value	0.541		0.363		0.059		**0.004**		0.339		0.821		**0.002**		0.035	
Colchicine compliance	Adherent (n=141)	69.6	12.2	66.5	23.6	73.6	18.2	63.0	24.9	83.0	16.4	73.3	22.6	52.7	28.0	58.7	23.2
	Non-adherent (n=30)	67.3	12.7	57.3	21.6	71.5	15.7	60.6	28.8	80.8	17.4	78.6	16.8	60.2	17.0	67.8	18.5
	P-value	0.358		**0.042**		0.554		0.641		0.520		0.143		0.157		**0.047**	
Number of attacks	No attack (n=72)	70.4	12.2	71.8	22.2	73.8	17.7	61.2	24.8	82.5	16.1	78.5	19.2	54.6	25.6	65.7	22.0
	1–2 attacks per year (n=66)	68.4	12.5	60.1	23.9	72.0	17.3	63.4	26.8	84.2	16.1	75.9	17.2	54.7	27.8	58.5	22.0
	>2 attacks per year (n=33)	68.1	12.0	59.5	22.3	74.4	19.2	64.2	25.3	79.7	18.4	79.7	17.0	51.1	26.3	52.4	23.3
	P-value	0.545		**0.004**		0.760		0.819		0.451		0.538		0.791		**0.014**	

KINDL: Kinder Lebensqualität Fragebogen; PW: Physical well-being; EW: Emotional well-being; SE: Self-esteem; FA: Family; FR: Friends; SC: School functioning; CG: Disease module; SD: Standard deviation; QoL: Quality of life.

nificant improvement in QoL scores in the 3rd month of anti-IL-1 therapy in adult FMF patients with severe disease activity.

The kid group patients had significantly lower KINDL QoL scores in self-esteem and significantly higher scores in school functioning compared to the kiddy group patients. These results suggest that FMF patients in the 8–16-year-old group have more difficulties with self-esteem, such as not feeling happy with themselves, than in the kiddy patient group. This may be seen in healthy adolescents as well. The older patients' perceptions about the course and complications of their disease are also different from those of younger patients. Makay et al. [4] reported lower QoL scores in FMF children who were non-adherent to colchicine than the adherent patients. Sahin et al. [10] reported that only the physical well-being scores were significantly lower in adult FMF patients who were non-adherent to colchicine therapy compared to the adherent patients. Our results were similar to this this report; when we compared the KINDL QoL scores of adherent and non-adherent patients to colchicine therapy, significantly higher physical well-being scores and lower disease module scores were found in the adherent group compared to the non-adherent group. We concluded that FMF patients who regularly use colchicine therapy every day feel physically better but also take the illness seriously and are more worried about their chronic disease. Sahin et al. [10] described no significant differences in the QoL domains in patients based on the number of attacks in adult FMF patients. However, we determined significantly lower scores in the physical well-being and disease module scores in the FMF children who experienced FMF attacks more than twice per year. These results suggest that pain and fever during FMF attacks were a concern for children with FMF and had a negative impact on physical well-being. For this reason, well-controlled disease activity is important for achieving a good QoL. Geographical region, living conditions, and educational status also affect the QoL of patients. Giese et al. [13] evaluated QoL in adult FMF patients living in Tur-

key and Germany and showed negative impacts in the physical health domain of QoL in patients living in both regions, compared to healthy controls. They also found that there was no correlation between QoL and disease activity in FMF patients.

The main limitation of this study is that it is a single-center study. However, patients coming from all regions of our country to the tertiary hospital provide diversity in the patients. There are limited data in the literature evaluating QoL and its association with clinical parameters in children with FMF. Most of these studies comprise small number of patients; however, our study has a higher number of children and adolescents evaluated for QoL.

Conclusion

This study suggests that the FMF patients had a significantly reduced QoL. The irregular use of colchicine and more frequent attacks affect QoL even more. Assessing QoL with multidisciplinary follow-up and controlling disease activity are essential, and if necessary, individualized support should be given to the patients.

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