Evaluation of Health-Related Quality of Life in Children and Adolescents with Familial Mediterranean Fever

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Abstract

Objective: Health-related quality of life (HRQOL) is a concept that assesses the effects of physical symptoms, functional status, and current illness on psychological and social functioning. In this study, we aimed to examine the quality of life in children and adolescents with familial Mediterranean fever (FMF) according to personal and disease-related factors.

Methods: A total of 257 children and adolescents with FMF aged 8–18 years were included in the study. The Juvenile Auto-inflammatory Disease Multidimensional Assessment Report was used for assessment of functional ability (self-report scale), pain (visual analog scale - VAS), therapeutic compliance, and HRQOL (physical, social, school, and emotional status). An increase in all subscale scores indicated a worsening.

Results: The mean age of the patients was 12.4±2.63 years, and 132 (51.4%) of them were women. In adolescents, HRQOL-general, -social, -school, and -emotional scores were higher than children ($p<0.001$ for all). Also, all HRQOL subscale scores of females were significantly higher than males ($p<0.05$ for all). Patients who had an attack in the last month had higher functional ability, pain, and all HRQOL subscale scores. However, patients with and without exertional leg pain had similar results in terms of all HRQOL subscales. The VAS pain score was positively correlated with HRQOL-general, -physical, -school, and -emotional scores. The therapeutic compliance scores were positively weakly correlated with all HRQOL subscales other than HRQOL-physical.

Conclusion: This study showed that the quality of life was worse in the adolescent age group, female gender, and the presence of attacks.

Keywords: Adolescents, children, familial Mediterranean fever, health-related quality of life

Ailesel Akdeniz Ateşi Olan Çocuk ve Ergenlerde Sağlıkla İlişkili Yaşam Kalitesinin Değerlendirilmesi

Öz

Amaç: Sağlıkla ilişkili yaşam kalitesi (SİYK), fiziksel semptomların, işlevsel durumun ve mevcut hastalığın psikolojik ve sosyal işlevsellik üzerindeki etkilerini değerlendiren bir kavramdır. Bu çalışmada, ailesel Akdeniz ateşi (AAA) olan çocuk ve ergenlerde yaşam kalitesini kişisel ve hastalıkla ilişkili faktörlere göre incelemeyi amaçladık.

Yöntem: Çalışmaya 8-18 yaşları arasında AAA tanılı 257 çocuk ve ergen dahil edildi. Fonksiyonel kapasite, ağrı (Görsel Analog Skala-GAS), tedavi uyumu ve SİYK (fiziksel, sosyal, okul, duygusal durum)'nin değerlendirmesinde özbildirime dayalı ''Otoinflamatuar Hastalığı olan Çocuklarda Çok Boyutlu Değerlendirme Ölçeği'' kullanıldı. Tüm alt boyutlarda puan artışı kötüleşmeyi ifade etmektedir.

Bulgular: Hastaların ortalama yaşı 12,4±2,63 yıldı ve 132'si (%51,4) kadındı. Ergenlerde genel, sosyal, okul ve duygusal SİYK alt ölçek puanları çocuklardan daha yüksekti (tümü için $p<0,001$). Ayrıca kadınların tüm SİYK alt ölçek puanları erkeklerden anlamlı derecede daha yüksekti (tümü için $p<0,05$). Ayrıca, son bir ay içinde atak geçiren hastalar daha yüksek fonksiyonel kapasite, ağrı ve SİYK alt ölçek puanlarına sahipti. Bununla birlikte, egzersiz bacak ağrısı olan ve olmayan hastalar, yine tüm SİYK alt ölçekleri açısından benzer sonuçlara sahipti. GAS-ağrı skoru, genel, fiziksel, okul ve duygusal durum SİYK skorlarıyla pozitif korelasyon göstermekteydi. Tedavi uyum skorları, fiziksel SİYK dışındaki tüm diğer alt ölçekler arasında pozitif yönde fakat zayıf bir korelasyon mevcuttu.

Sonuç: Bu çalışma, ergen yaş grubu, kadın cinsiyet ve devam eden atakların varlığında yaşam kalitesinin daha kötü olduğunu gösterdi.

Anahtar Kelimeler: Ergenler, çocuklar, ailesel Akdeniz ateşi, sağlıkla ilişkili yaşam kalitesi

Familial Mediterranean fever (FMF) is the most common monogenic auto-inflammatory disease and usually occurs with recurrent, self-limiting attacks of polycerositis and arthritis [1]. FMF is highly prevalent in societies of Eastern Mediterranean origin, including Jews, Turks, Armenians, and Arabs. In our country, more than on the Mediterranean coasts, it is more common

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in people whose roots are mainly in Sivas, Kastamonu, Tokat, Sinop, Ordu, Samsun, and, especially, in the Black Sea, Central Anatolia, and Eastern Anatolia [2]. The MEFV gene responsible for FMF etiology is located on chromosome 16p13.3 and is responsible for the production of a 781 amino acid protein called pyrin (marenostrin) [3]. Although the clinical findings during attacks may vary, the most common attack type is a combination of fever, abdominal pain, and joint findings [4]. Patients may also have symptoms not related to attacks, such as prolonged myalgia, exertional leg pain, post-exercise erysipelas-like erythema, and sacroileitis [5]. Colchicine is the main treatment option and is very effective in reducing the frequency of attacks and preventing amyloidosis [6].

The quality of life (QoL) is defined as a way of perceiving one's own situation within the culture and value system [7]. To evaluate QoL, the general quality of life scales, which can be used in both healthy and sick individuals, and health-related QoL (HRQOL) scales developed for chronic diseases are used [8]. HRQOL is a concept that includes the assessment of physical symptoms, functional status, and the effects of the disease on psychological and social functioning [9, 10]. The fact that disease-related QoL scales are specific for a current disease increases internal consistency, specificity, and sensitivity [8]. It is essential to evaluate QoL to clearly understand the effects of diseases on children [11]. Moreover, improving the QoL in children and adolescents with chronic diseases is a very important long-term goal in pediatric rehabilitation [12].

In the literature, it has been reported in several studies that use the general QoL scales that child-adolescent and adult patients with FMF have impaired QoL compared with healthy people [13-15]. In this study, we aimed to evaluate the QoL using the disease-specific scale according to demographic and clinical characteristics in a large sample of children and adolescents with FMF.

Material and Methods

Participants and procedure

This single center, cross-sectional study included 257 children and adolescents aged 8–18 years who were consecutively admitted to the Pediatric Rheumatology outpatient clinic of Istanbul University - Cerrahpasa, Cerrahpasa Medical School, between March and September, 2017, and were followed up and treated for FMF for at least six months. Participants who were illiterate, had psychiatric diseases, and any known chronic diseases other than FMF were excluded from the study. The diagnosis of FMF was made by an experienced pediatric rheumatologist according to the Turkish Pediatric FMF criteria (having two or more criteria of fever lasting 6–72 hours, abdominal pain, chest pain, oligo-arthritis, positive family history, and having at least three attacks) [16].

Measures

Socio-demographic data form

This data form prepared by the researchers consisted questions about the child's age, sex, and education status; parents' age and education status; family integrity; economic status; age at disease onset and age at diagnosis, number of attacks in the past year, regular drug use, and blood sample results.

Juvenile auto-inflammatory disease multidimensional assessment report (JAIMAR)

This scale was developed in Turkish by Konukbay et al. [17] who also performed its validity and reliability study. It measures four dimensions, including functional ability, pain (visual analog scale [VAS]), therapeutic compliance, and HRQOL (physical, social, school, and emotional status) in auto-inflammatory diseases. Functional ability assesses the patients' condition in the last FMF attack. The scores range from 2.5 to 10, and an increased score indicates a worsening. Pain is scored subjectively between 0 and 10 using VAS, and higher scores indicate a worsening of pain. Finally, the scores of therapeutic compliance and HRQOL dimensions range from 2 to 10. As the scores get higher, drug compliance and QoL decrease. For the JAIMAR's dimensions, the Cronbach's alpha internal consistency reliability coefficients were found to be 0.507–0.998. In this study, the 8–18 aged self-report form of the scale was used.

Ethical approval

The study was approved by the local ethics committee of İstanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine (decision no: 95559 dated March 09, 2017). All the procedures performed in the study involving human participants were in accordance with ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All the participants were informed of the study protocol and those who volunteered to participate were included in the study. In the study, all children were over 8 years of age and were literate, and they signed the informed consent form together with their parents.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS Corp.,

Armonk, NY, USA) software (version 21.0). Data were first analyzed for normality using the Shapiro-Wilk test. Frequencies were compared using Pearson's and Fisher's exact tests. Continuous variables were expressed as mean±standard deviation (SD). Because the data did not conform to normal distribution, the groups were compared using the Mann–Whitney U test, and Spearman's rank order test was used to calculate the correlation coefficients between the continuous variables. The results were evaluated at 95% confidence interval, and a $p<0.05$ was considered statistically significant.

Results

Participants' demographic and clinical characteristics

Among 257 patients, 132 (51.4%) were women. The mean age of the patients was 12.4±2.63 years. The majority of the patients (85.6%) lived in a nuclear family. The mean age of onset of FMF symptoms was 4.56±3.17 years, and the mean age at diagnosis was 6.86±3.21 years. The general socio-demographic characteristics of the patients are shown in Table 1.

Although no FMF attacks were observed in 122 (47.5%) patients in the past one year, 13 (5.1%) had more than 13 attacks per year, and 60 (23.3%) had an FMF attack in the past month. Of these patients, 39 (29.5%) were women and 21 (16.8) men. There was a statistically significant difference (p=0.016). The frequency of women (59.1%) who had an attack in the past year was higher than men (45.6%) (p=0.030). When the patients were compared in terms of age, children and adolescents had similar rate of FMF attacks in the past month (23.8% and 22.8%, respectively; p=0.848). During FMF attacks, 224 (87.2%) patients stated that they experienced abdominal pain, 46 (17.9%) had chest pain, 42 (16.3%) had arthritis, and 173 (67.3%) had arthralgia. One hundred and eighteen (45.9%) patients had exertional leg pain during non-attack periods. None of the patients had renal involvement during FMF. Although all the patients received colchicine, anakinra was added to the colchicine treatment in only five patients owing to refractory disease.

Comparisons of scale scores among subgroups

When children (≤12 years) and adolescents (>12 years) with FMF were compared, there was no significant difference between them in terms of functional ability, pain, and HRQOL-physical. However, the adolescents' therapeutic compliance was worse than those of children (3.95±1.44 vs. 3.17±1.24, p<0.001). In addition, HRQOL (general, social, school, and emotional) scores were higher in adolescents than in children (p<0.001 for all).

Table 1. Socio-demographic characteristics of participants

Variables	Mean±SD or n (%)
Age (years)	12.4±2.63
Sex	
Male	125 (48.6)
Female	132 (51.4)
Age at disease onset, years	4.56±3.17
Age at diagnosis, years	6.86±3.21
Education status (child), years	6.86±2.46
Maternal age, years	39.16±5.18
Education status (mother), years	7.93±3.78
Paternal age, years	42.87±5.51
Education status (father), years	8.69±3.96
Family structure	
Nuclear family	220 (85.6)
Extended family	26 (10.1)
Single parent	11 (4.3)
Income levels, monthly	
< 1,500 Turkish Liras	32 (12.5)
1,500–4,500 Turkish Liras	184 (1.6)
> 4500 Turkish Liras	41 (16)

When patients were compared in terms of sex, women and men had similar results for therapeutic compliance (p=0.756). However, functional ability, pain, and all HRQOL subscale scores of women were significantly higher than of men (p<0.05 for all).

Sixty (23.3%) patients had an attack in the past month. There was no difference in therapeutic compliance between patients who had an attack and those who did not have an attack in the past month; however, patients who had an attack had higher functional ability, pain, and all HRQOL subscale scores. Similarly, except for the HRQOL-social, all HRQOL subscale, functional ability, and pain scores of 135 (52.5%) patients who had an attack were significantly higher than the patients who did not have an attack in the past year.

One hundred and eighteen (45.9%) patients had exertional leg pain during the attack-free periods, and these patients had higher pain scores than those without (3.24±3.19 vs. 2.39±2.98, p=0.018). However, patients with and without exertional leg pain had similar results in terms of functional ability, therapeutic compliance, and all HRQOL subscales (p>0.05 for all). The

Table 2. Comparison of scale scores according to demographic and clinical characteristics

Characteristics		Functional ability	VAS Pain	Therapeutic compliance	HRQOL General	HRQOL Physical	HRQOL Social	HRQOL School	HRQOL Emotional
Age	≤12 years (n=130)	3.25±1.35	2.96±3.21	3.17±1.24	3.50±1.07	3.35±1.53	2.83±1.24	3.73±1.24	3.61±1.31
	>12 years (n=127)	3.23±1.25	2.59±2.99	3.95±1.44	4.10±1.37	3.31±1.42	3.46±1.49	4.55±1.62	4.32±1.66
	p	0.849	0.377	<0.001	<0.001	0.866	<0.001	<0.001	<0.001
Sex	Female (n=132)	3.50±1.52	3.38±1.52	3.59±1.48	4.12±1.42	3.68±1.65	3.40±1.56	4.41±1.58	4.33±1.74
	Male (n=125)	2.96±0.94	2.14±2.98	3.52±1.31	3.45±0.97	2.96±1.17	2.87±0.98	3.85±1.34	3.45±0.97
	p	0.001	<0.001	0.756	<0.001	<0.001	0.034	0.004	0.001
An attack in the past month	Yes (n=60)	3.81±1.57	6.14±2.82	3.58±1.69	4.55±1.33	4.45±1.94	3.58± 1.67	5.01±1.46	4.63±1.63
	No (n=197)	3.06±1.15	1.75±2.37	3.58±1.69	3.56±1.15	2.99±1.11	3.01±1.19	3.87±1.40	3.76±1.45
	p	<0.001	<0.001	0.538	<0.001	<0.001	0.02	<0.001	<0.001
An attack in the past year	Yes (n =135)	3.52±1.51	4.05±3.26	3.72±1.53	4.13±1.33	3.72±1.70	3.27±1.41	4.62±1.48	4.27±1.63
	No (n=122)	2.92±0.92	1.36±2.17	3.37±1.22	3.42±1.08	2.90±1.04	2.99±1.23	3.60±1.33	3.62±1.34
		<0.001	<0.001	0.065	<0.001	<0.001	0.096	<0.001	<0.001
Exertional leg pain	Yes (n=118)	3.21±1.17	3.24±3.19	3.63±1.55	3.91±1.24	3.43±1.39	3.28±1.46	4.21±1.45	4.09±1.53
	No (n=139)	3.26±1.40	2.39±2.98	3.49±1.26	3.69±1.28	3.25±1.56	3.02±1.21	4.07±1.53	3.85±1.53
	p	0.296	0.018	0.904	0.078	0.094	0.171	0.306	0.132

VAS: visual analog scale; HRQOL: health-related quality of life

comparisons of scale scores among these demographic and clinical subgroups are summarized in Table 2.

Correlation analyses of some study variables

There was a weak positive correlation between the patients' age and the HRQOL (general, social, school, and emotional) subscale scores. The VAS pain score was positively moderately correlated with HRQOL-general (r=0.395, p<0.001), HRQOL-physical (r=0.489, p<0.001), HRQOL-school (r=0.360, p<0.001), and HRQOL-emotional (r=0.303, p<0.001) scores. In addition, there was a weak positive correlation between VAS pain and HRQOL-social (r=0.194, p<0.01). The therapeutic compliance scores had a weak positive correlation with all the HRQOL subscales, other than HRQOL-physical. However, there was a positive correlation between the HRQOL-general and other HRQOL subscale scores, ranging from moderate to strong. Finally, CRP and ESR (erythrocyte sedimentation rate), which are acute phase reactants, did not correlate with functional ability, pain, therapeutic compliance, and all the HRQOL subscale scores. The inter-correlation among some variables are detailed in Table 3.

Discussion

In this study, we showed that patients with an FMF attack in the past one month had a worse QoL. Similarly, the QoL was worse in patients who had an attack in the past one year. Moreover, men had a better QoL than women, and adolescents' therapeutic compliance and all HRQOL dimensions, except the physical one, were worse than children.

In our study, the age of onset of FMF was 4–5 years, and the age at diagnosis was 6–7 years. However, in a multi-center study conducted in Turkey, the age of onset and the age at diagnosis were reported as 9–10 years and 16–17 years, respectively [18]. However, this study was conducted with the inclusion of adults as well as children. There may be a higher age of onset and age at diagnosis because of the presence of patients with late onset and delayed diagnosis. When the literature on FMF symptoms during attacks is reviewed, varying rates have been reported in different studies. For example, in one of the studies, the authors have reported that 98.6% of the patients had abdominal pain, 17.7% had chest pain, 20.4% had arthritis, 59.9% had arthralgia [19]. In another study, the authors

Table 3. Correlation analyses of some study variables

	2	3	4	5	6	7	8	9	10	11	12
1. Age	–0.002	–0.043	0.332‡	0.208‡	–0.58	0.139†	0.244‡	0.227‡	0.451‡	–0.005	–0.119
2. Functional ability		0.217‡	0.166†	0.434‡	0.474‡	0.361‡	0.381‡	0.320‡	0.006	0.062	0.039
3. VAS pain			0.007	0.395‡	0.489‡	0.194†	0.360‡	0.303‡	0.109	0.106	0.082
4. Therapeutic compliance				0.230‡	0.058	0.218‡	0.204‡	0.242‡	0.208‡	0.051	0.018
5. HRQOL-general					0.670‡	0.701‡	0.814‡	0.935‡	0.131*	0.004	–0.003
6. HRQOL-physical						0.443‡	0.505‡	0.512‡	0.067	0.003	0.021
7. HRQOL-social							0.517‡	0.584‡	0.164†	–0.002	–0.091
8. HRQOL-school								0.646‡	0.188†	0.088	–0.021
9. HRQOL-emotional									0.097	–0.035	0.021
10. Duration of FMF										0.054	–0.041
11. CRP											0.522‡
12. ESR											

The correlation coefficients are shown. All of these study variables were analyzed using univariate methods.
*p<0.05; †p<0.01; ‡p<0.001
VAS: visual analog scale; HRQOL: health-related quality of life; FMF: familial Mediterranean fever; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate

have found that 89.2% of the patients had abdominal pain, 17.2% had chest pain, 40.7% had arthritis, and 66% had exertional leg pain [20]. In our study, we evaluated the symptoms during the attack according to parental reports. The reasons why arthritis was less common in our study may be because of the ignorance of the parents, misinterpretation of symptoms, or the inability to remember because the majority of the patients had decreased number of attacks with colchicine and did not have attacks for a long time.

The scales based on self-reports and parental reports can be used to evaluate the QoL in children and adolescents. The weaknesses of the parental reports can be explained as follows: parents do not clearly know the child's symptoms; peer relationships or concerns about the future; are affected by other children when filling out the forms; and are affected by their own expectations and hopes, present stress, or mental state [8, 21, 22]. As our aim in this study was to reveal the QoL of children and adolescents with FMF as a result of subjective evaluations, a self-report form was used.

Although the rate of patients with an attack in the past one month was similar between children and adolescents; all HRQOL dimensions, except the physical one, and therapeutic compliance were worse in adolescents. Makay et al. [13] found that the social QoL was better in adolescents than in children, and there was no difference in other areas; however, in this study, the sample size was low, and the frequency of attacks by age was not evaluated. Increased self-control with adolescence and decreased parental control may explain worse therapeutic compliance in the adolescents in our study. Furthermore, during adolescence, the increase in importance of peer interactions and social environments may cause the social, emotional, and school-related QoL to be more affected than in children. In our study, the pain scores of women were higher, and their QoL was worse than men. In a study conducted with children and adolescents with FMF, no difference was found between men and women in terms of QoL [13]. These sex-specific differences in QoL may be because of the effects of different factors, such as social support, cultural factors, and psychological resilience.

It is known that the deterioration in psychosocial well-being increases when chronic diseases cause limitations in daily life [23]. In our study, the QoL of patients who had an FMF attack in the past one month was poor in all HRQOL dimensions. Because patients with FMF are usually asymptomatic during attack-free periods, recent attacks may cause limitations in daily life and negatively affect QoL. In addition, patients with an attack in the past one year had worse outcomes than those who did not experience any in all HRQOL dimensions, except the social one. Approximately, half of the patients with FMF who had an attack in the past one year also had an attack in the past one month. However, exertional leg pain can be seen during attack-free periods also and may cause physical limitations in daily life. Nevertheless, there was

no difference between the QoL in patients with and without exertional leg pain. It can be said that patients with FMF experiencing severe pain during attacks may cause them to be less affected by exertional leg pain during attack-free periods. These findings suggest that the deterioration in HRQOL cannot be explained only by the presence of attacks and physical limitations. The accompanying psychological symptoms, such as depression and anxiety, family relationships, and social support, may have an impact on the HRQOL.

Poor drug adherence, which is frequently encountered in children with chronic and auto-inflammatory diseases, may cause higher morbidity and mortality along with other adverse events [24]. In a previous study, it has been shown that QoL is worse in the presence of treatment non-compliance in patients with FMF [13]. In our study, consistent with the literature, QoL decreased as therapeutic compliance deteriorated. However, Makay et al. [13] have found no correlation between the duration of FMF and QoL. In our study, there was a significant correlation, but the association was weak.

The strengths of our study were the large sample size and the use of a disease-specific QoL scale. However, the absence of a control group can be considered an important limitation. Another limitation of our study was that factors such as psychological symptoms, family relationships, social support, and resilience were not examined, and only QoL was evaluated.

We demonstrated that QoL was worse not only in patients with FMF attack in the past one month but also in those who had an attack in the past one year. We also demonstrated that QoL did not change depending on the presence or absence of exertional leg pain, which is a symptom during attack-free periods. We found that women had a worse QoL than men and that therapeutic compliance was associated with QoL. Recently, QoL has become increasingly important as an indicator of response to treatment and improvement. Therefore, new studies that will provide a better understanding of environmental and personal factors other than illness (such as psychological symptoms, family relationships, social support, and psychological resilience) that may affect HRQOL will guide clinicians.

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