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Original Article

Assessing fatigue and related factors in adolescents with familial Mediterranean fever (FMF): psychometric properties of the PedsQL Multidimensional Fatigue Scale

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ABSTRACT

Background. Fatigue is a common problem in pediatric rheumatic diseases and is associated with poor quality of life. However, no validated methods are available to measure fatigue in adolescents with familial Mediterranean fever (FMF). The aim of the study was to establish validity and reliability for the child self-report PedsQL Multidimensional Fatigue Scale (PedsQL-MFS) and to investigate the effects of physical characteristics, disease-related characteristics, sleep quality/duration, and the amount of physical activity on fatigue in adolescents with FMF.

Methods. Seventy-one adolescents with FMF (13-18 years) were included. Children were examined regarding physical- and disease-related characteristics and completed patient-reported outcome measures (PROMs) regarding sleep quality/duration, physical activity levels, and fatigue. PedsQL-MFS was re-completed within the following 7-14 days.

Results. PedsQL-MFS demonstrated excellent test-retest reliability (ICC in 95% CI: 0.877-0.958) and internal consistency (Cronbach's α: 0.928). All items contributed to the total score (item-total correlation >0.3). PedsQL-MFS scores were significantly correlated to fatigue (r: -0.666, p<0.001), physical activity (r: 0.373, p<0.001), sleep quality (r_s: 0.678, p<0.001), and sleep duration (r: 0.473, p<0.001). Being female, having attacks in the last six months, a sleep duration of less than seven hours, and engaging in less physical activity resulted in higher fatigue.

Conclusions. PedsQL-MFS seems to be feasible for assessing fatigue in adolescents with FMF. Sex, recent attacks, sleep, and physical activity should be taken into consideration in the fatigue management of patients with FMF.

Key words: Fatigue, child, familial Mediterranean fever, sleep, physical activity.

Familial Mediterranean fever (FMF) is the most prevalent monogenic auto-inflammatory disease.[1,2] It is especiailly common in people living in/originating from the Mediterranean basin and the Middle East.[1,2] However, the incidence of FMF is on the rise all over the world as a result of migrations, and FMF is being diagnosed more frequently in regions where the disease was thought to be uncommon such as Europe, Japan, and United States.[3-5] The disease onset is usually during childhood and progresses with recurrent attacks characterized by fever, peritonitis, pleuritis, arthritis/arthralgia, or erysipelas-like skin findings.[1,2] Patients are usually considered symptom-

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free between attacks. However, subclinical inflammation and chronic disease course may have a negative impact on the quality of life even between attacks.[6-8]

Fatigue is defined as a persistent feeling of exhaustion and lack of energy which can originate from physical, mental/emotional, sleep-related, and disease-related factors.[9-11] Moderate to severe fatigue is reported in pediatric and adult patients with different chronic conditions including rheumatic diseases and is a debilitating factor that affects many aspects of daily living and physical functioning.[10,12-14] Concurringly, European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology (ACR) recommend assessing fatigue as a part of regular follow-up in rheumatic and musculoskeletal diseases.[15,16] To the best of our knowledge, solely Ozdel et al.[17] attempted to evaluate fatigue with an unvalidated questionnaire previously and reported that children with FMF presented higher fatigue perception than their healthy peers. However, a more comprehensive evaluation of fatigue using valid and reliable tools may help to better understand the impact of fatigue in children with FMF.

The PedsQL Multidimensional Fatigue Scale (PedsQL-MFS) is a self-report outcome measure, developed to assess fatigue in children of different age groups.[18] The psychometric properties of PedsQL-MFS were demonstrated to be adequate in various conditions such as cancer, obesity, juvenile idiopathic arthritis, juvenile systemic lupus erythematosus, and juvenile fibromyalgia.[18-20]

This study aimed to (a) investigate the psychometric properties of PedsQL-MFS, and (b) compare fatigue according to sex, disease-related factors, sleep duration, and physical activity in adolescents with FMF.

Material and Methods

This was a cross-sectional validation study. The ethical approval was obtained from the Non-Interventional Clinical Studies Institutional Review Board of İzmir Katip Çelebi University (date: 24.06.2021, number: 0308). All procedures were performed in accordance with the Declaration of Helsinki. Adolescents and their parents signed a written informed consent prior to their participation.

Participants

G*Power 3.1.9.4 software was used to calculate the sample size. An expected minimum correlation coefficient of 0.3, a minimum type I error of 0.05, and a maximum type II error of 20% revealed that at least 64 participants were necessary to explore the convergent validity of PedsQL-MFS.

Adolescents (aged 13-18 years) diagnosed with FMF based on Turkish pediatric FMF criteria[21] were included in the study between July 2021 and July 2022. Exclusion criteria were (a) concomitant conditions such as fibromyalgia or other systemic diseases that cause fatigue, (b) intra-articular injection and/or surgery in the last six months.

Procedures

Adolescents who met the eligibility criteria were invited to participate. Physical characteristics (age, sex, body-mass index), and clinical parameters (*MEFV* mutation type, time since the onset of the symptoms, time since diagnosis, the dosage of colchicine and/or other medication, and the number of FMF attacks in the last six months) were recorded on a structured form. Subsequently, adolescents filled out the PedsQL-MFS child self-report[20], The Checklist Individual Strength (CIS)[22], Sleep Quality Scale and Sleep Variables Questionnaire (SQS-SVQ)[23], and Children's Leisure Assessment Scale (CLASS).[24] All assessments were

completed within the same day. All adolescents re-completed PedsQL-MFS within the following 7-14 days.

Outcome measures

The PedsQL Multidimensional Fatigue Scale (PedsQL-MFS): The Turkish translation of PedsQL-MFS, along with other languages was provided by the original author Varni under the license of Mapi Research Trust Organization. Permission to use the Turkish version of PedsQL-MFS was obtained from Mapi Research Trust Organization prior to the study. PedsQL-MFS has separate forms for different age categories. PedsQL-MFS for children between 13-18 years of age were administered to adolescents (child self-report) in the present study.[20] PedsQL-MFS included 18 identical items under three sub-categories: (1) General Fatigue, (2) Sleep/ Rest Fatigue, and (3) Cognitive Fatigue. Each sub-category included six items, and each item was scored on a 5-point Likert scale between zero (the absence of a problem in during the past month) and four (the problem was almost always present during the past month). The item scores were reversed and were linearly transformed into a score between 0 and 100 (0=100, 1=75, 2=50, 3=25, 4=0). The total score and sub-category scores were calculated by summing up item scores and dividing the outcome by the number of items. The final score ranged between 0-100 with higher scores indicating less fatigue.

The Checklist Individual Strength (CIS): CIS was employed to examine the convergent validity of the PedsQL. CIS was used to assess fatigue in children with FMF previously.[17] CIS scores were investigated in four sub-categories: (1) Subjective Fatigue (eight items), (2) Concentration (five items), (3) Motivation (four items), and (4) Physical Activity (three items). CIS consisted of 20 fatigue-related items (e.g., "*I feel tired*") scored on a 7-point Likert scale (between 1: "yes, it is true", and 7: "no, it is false"). Eleven out of the 20 items were reverse scored. The total score and sub-category scores were calculated by summing up the scores. Higher scores indicated a higher perception of fatigue.[22]

Sleep Quality Scale and Sleep Variables Questionnaire (SQS-SVQ): SQS-SVQ included a total of 15 items and was used to measure the quality of sleep (0-21, higher scores indicating better sleep quality) and total time spent sleeping (in minutes) in the present study. The calculations for each component were performed following the instructions by Onder et al.[23]

Children's Leisure Assessment Scale (CLASS): CLASS was used to determine the level of physical activity.[24] CLASS consisted of 45 items of which 31 questions physical activities (e.g., swimming, dancing, walking, etc.) and 14 questions sedentary behaviors (e.g., watching TV, listening to music, etc.). Responders indicated "yes" or "no" representing whether they performed the relevant activity on a typical week. Children who marked "yes" for a particular item were also inquired regarding frequency and total time (in minutes or hours). The option "other" was provided for activities/ behaviors which were not included in the questionnaire but were performed by children. The energy expenditure for each physical activity was calculated using the formula: *(METs of an activity)*(minutes spent in doing the activity in a week)* with the metabolic equivalent (MET) values provided by Ainsworth et al.[25] The total physical activity was computed by summing up the METs calculated for each item. Higher MET values indicated a higher level of physical activity.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (Armonk, NY, USA). The normality of the data was analyzed by examining the Kolmogorov-

Smirnov test, histograms, detrended Q-Q plots, and skewness/kurtosis values. Mean and standard deviations or median and interquartile ranges were used depending on the distribution of the data. Categoric variables were expressed as numbers (n) and percentages (%). The missing data was handled as suggested by Varni et al.[18] $p<0.05$ was considered statistically significant.

Reliability: The reliability of PedsQL-MFS was explored by analyzing corrected item-total correlation, and internal consistency (Cronbach's α). A change of less than 10% in internal consistency with the exclusion of items, and a correlation coefficient higher than 0.3 in item-total correlation were assumed to keep any individual item. Intraclass Correlation Coefficients 2,1 (ICC) were calculated to establish test-retest reliability.

Validity: Convergent validity of PedsQL-MFS was investigated by calculating correlation coefficients between PedsQL-MFS and CIS, CLASS, and SQS-SVQ results. Pearson (r) and Spearman (r_s) correlation coefficients were calculated for normally and non-normally distributed variables, respectively. Obtained correlations were interpreted as follows: negligible=0 to 0.29, poor=0.30 to 0.49, moderate=0.50 to 0.69, good=0.70 to 0.89, and excellent=0.90 to 1.00.[26]

Sub-group comparisons: Mann-Whitney U test was employed to compare fatigue among different sub-groups according to physical characteristics (sex), disease-related characteristics (number of attacks, colchicine use, presence of M694V mutation), and other variables (sleep duration, level of physical activity). Cohen's d (*d)* values were calculated for estimating effect size.[27] Effect sizes were interpreted as follows: $d<0.2$=negligible, $0.2\leq d<0.5$=small, $0.5\leq d<0.8$=moderate, $0.8\leq d<1.3$=large, $1.3\leq d$=very large. Seven hours of sleep and 2560 MET-min/week of physical activity were used as cut-off values to divide patients into sub-groups. Seven hours of sleep was recommended by Leger et al.[28] and 2560 MET-min/week was calculated using the equation *60 minutes*7 days*6 MET=2560* based on the recommendation of at least 60 minutes of moderate to vigorous activity (4-8 METs) every day for individuals under the age of 18 years by the World Health Organization.[29]

Results

The study was completed with the participation of 71 adolescents with FMF. Re-test data was obtained from 51 adolescents. The number of missing items was detected as minimal (0.5%). The results regarding physical characteristics, disease-related characteristics, and PROMs were presented in Table I.

The internal consistency of PedsQL-MFS was excellent (Cronbach's α: 0.928). No significant change was observed in internal consistency with the exclusion of any item (change <10%), and all the items contributed to the total score (item-total correlation >0.3), (Table II). The test-retest reliability was determined as good to excellent (ICCs: between 0.881 and 0.928, $p<0.05$) for total- and sub-scores (Table III).

Significant poor to good correlations were observed between PedsQL-MFS and CIS total score (r: -0.666, $p<0.001$), physical activity levels (r: 0.373, $p<0.001$), sleep quality (r_s: 0.628, $p<0.001$), and sleep duration (r_s: 0.473, $p<0.001$) indicating the convergent validity of PedsQL-MFS (Table IV).

PedsQL-MFS scores were lower; in females (d=0.77, $p<0.05$), in children who had attacks in the last six months (d=0.85, $p<0.05$), in children who were sleeping less than seven hours a day (d=0.94, $p<0.001$), and in children who engaged in less than 2560 MET-min/week of physical activity (d=0.59, $p<0.05$), (Table V). No between-group differences were detected in PedsQL-MFS scores according to colchicine use or the presence of M694V mutation ($p>0.05$), (Table V).

Table I. Demographic and disease-related characteristics of children with Familial Mediterranean Fever.

	Median (Q1-Q3) or n (%) (n=71)
Sex (Female/Male), n	34/37
Age, yr	15 (14-16)
BMI (kg/m^2)	20.11 (18.65-23.48)
Time since the onset of symptoms, yr	10 (7-14)
Time since the diagnosis, yr	9 (6-11)
Number of attacks in last six months, n	1 (0-3)
Colchicine	
Not using, n (%)	12 (16.9%)
0.5 mg/day, n (%)	8 (11.3%)
1 mg/day, n (%)	23 (32.4%)
1.5 mg/day, n (%)	18 (25.4%)
2 mg/day, n (%)	10 (14.1%)
MEFV mutations	
Undefined	21 (29.6%)
M694V Homozygous	15 (21.1%)
M694V Heterozygous	13 (18.3%)
R202Q Homozygous	3 (4.2%)
E148Q Homozygous	1 (1.4%)
E148Q Heterozygous	1 (1.4%)
P369S Heterozygous	1 (1.4%)
E148Q/V726A Heterozygous (Compound)	1 (1.4%)
E148Q/M964M Heterozygous (Compound)	1 (1.4%)
E148Q/R202Q Heterozygous (Compound)	3 (4.2%)
K695R/R202Q Heterozygous (Compound)	1 (1.4%)
M6801/M694V Heterozygous (Compound)	1 (1.4%)
M694V/R202Q Heterozygous (Compound)	3 (4.2%)
M694V/R202Q Homozygous (Compound)	1 (1.4%)
M694V Heterozygous/R202Q Homozygous (Compound)	1 (1.4%)
M694V/E148Q Heterozygous (Compound)	2 (2.8%)
M694V/M6801 Heterozygous (Compound)	1 (1.4%)
M696V/R202Q Homozygous (Compound)	1 (1.4%)
CIS	
Subjective fatigue (score: 0-56)	27 (20-35)
Concentration (score: 0-35)	18 (12-22)
Motivation (score: 0-28)	15 (10-18)
Activity (score: 0-21)	10 (7-13)
Total (score: 0-140)	73 (54-83)
CLASS	
Total physical activity (METs min/week) (n=61)	2585 (986-5155)
SQS-SVQ	
Sleep quality (score: 0-21)	15 (13-17)
Sleep duration (min/day)	466 (405-510)

CIS: The Checklist Individual Strength, CLASS: Children's Leisure Assessment Scale, SQS-SVQ: Sleep Quality Scale and Sleep Variables Questionnaire, MET: metabolic equivalent, Q1-Q3: first and third quartiles.

Table II. Item-Total Correlations of PedsQL-MFS.

Item	Corrected Item-Total Correlation	Cronbach's Alpha if Item Deleted
General Fatigue 1	0.707	0.922
General Fatigue 2	0.620	0.924
General Fatigue 3	0.757	0.921
General Fatigue 4	0.623	0.924
General Fatigue 5	0.703	0.922
General Fatigue 6	0.746	0.921
Sleep/Rest Fatigue 1	0.489	0.927
Sleep/Rest Fatigue 2	0.586	0.925
Sleep/Rest Fatigue 3	0.618	0.924
Sleep/Rest Fatigue 4	0.338	0.930
Sleep/Rest Fatigue 5	0.529	0.926
Sleep/Rest Fatigue 6	0.553	0.926
Cognitive Fatigue 1	0.741	0.921
Cognitive Fatigue 2	0.608	0.924
Cognitive Fatigue 3	0.697	0.922
Cognitive Fatigue 4	0.479	0.927
Cognitive Fatigue 5	0.728	0.922
Cognitive Fatigue 6	0.670	0.923
		Total Cronbach's alpha= 0.928

Table III. Test-retest reliability of PedsQL-MFS.

	Test (Mean±SD) (n=51)	Re-test (Mean±SD) (n=51)	ICC (95% CI)
Child self-report			
General Fatigue	60.87±26.72	60.86±24.21	0.909 (0.846-0.947)
Sleep/Rest Fatigue	56.51±21.65	57.43±22.53	0.899 (0.829-0.941)
Cognitive Fatigue	68.89±23.84	71.24±22.50	0.881 (0.801-0.930)
Total	62.09±20.89	63.18±20.09	0.928 (0.877-0.958)

CI: confidence interval, ICC: Intraclass correlation coefficient, SD: standard deviation.

Table IV. Convergent validity of PedsQL-MFS.

n=71	PedsQL-MFS			
	General	Sleep/Rest	Cognitive	Total
CIS				
Subjective fatigue	-0.719**#	-0.546**#	-0.414**#	-0.652**#
Concentration	-0.528**#	-0.210#	-0.555**#	-0.540**#
Motivation	-0.517**#	-0.356*#	-0.292*#	-0.465**#
Activity	-0.459**#	-0.292*#	-0.320*#	-0.418**#
Total	-0.714**†	-0.483**†	-0.511**†	-0.666**†
CLASS				
Total physical activity (METs min/week)	0.397**†	0.208†	0.324*†	0.373**†
SQS-SVQ				
Sleep quality (score: 0-21)	0.647**#	0.555**#	0.429**#	0.628**#
Sleep duration (min/day)	0.438**†	0.513**†	0.287†	0.473**†

CIS: The Checklist Individual Strength, CLASS: Children's Leisure Assessment Scale, SQS-SVQ: Sleep Quality Scale and Sleep Variables Questionnaire, mins: minutes

#: Spearman's correlation coefficient

†: Pearson's correlation coefficient

*: p<0.05, **: p<0.001

Table V. Comparison of fatigue according to demographic, disease-related or physical characteristics.

		PedsQL-MFS Median (Q1-Q3)	*p**	*d*
Sex	Female (n= 34)	56.9 (38.9-68.4)	*0.002*	0.77
	Male (n= 37)	69.4 (59.0-79.9)		
Attacks in last six months	0 (n= 33)	75.0 (53.8-83.3)	*0.004*	0.85
	≥1 (n= 38)	63.2 (43.4-67.0)		
Colchicine	Not using (n=12)	64.6 (43.4-79.1)	*0.836*	-
	Using (n=59)	65.7 (46.5-76.7)		
M694V mutation	Present (n=38)	66.3 (41.3-74.7)	*0.331*	-
	Not present (n=12)	64.6 (49.7-87.5)		
Sleep duration	<7 hours (n=21)	44.4 (30.5-76.3)	*<0.001*	0.94
	≥7 hours (n=48)	68.1 (53.5-82.6)		
Total physical activity	≥2560 MET-min/week (n=31)	67.8 (54.2-77.8)	*0.025*	0.59
	<2560 MET-min/week (n=30)	53.5 (38.9-75.3)		

MET: metabolic equivalent, min: minute, d: Cohen's *d* (effect size), Q1-Q3: first and third quartiles.
*: Mann-Whitney U test

Discussion

The present study was the first to present the psychometric properties of PedsQL-MFS in children with FMF. PedsQL-MFS demonstrated good validity and reliability. Being female, having attacks in the last six months, sleeping less than seven hours, and engaging in less physical activity had a negative impact on fatigue. On the other hand, the presence of M694V mutation or colchicine usage showed no significant impact on fatigue.

The rates of missing data were at an acceptable level and similar to previously reported values[20] indicating PedsQL-MFS is feasible in children with FMF. The ICC values were in general agreement with the results of previous studies that investigated the reliability of PedsQL-MFS in children with rheumatic diseases.[20] As there were no validated gold standard tools to evaluate fatigue in children with FMF, we could not examine the concurrent validity of PedsQL-MFS. Additionally, the ability to discriminate children with FMF from healthy children in terms of fatigue or sensitivity/specificity in detecting patients with and without fatigue were not investigated due to absence of a control group and a relatively small sample size. Thus, these psychometric properties of PedsQL-MFS are yet to be investigated in the future.

Fatigue has been inadequately investigated in children with FMF. Best to our knowledge, only the study by Ozdel et al.[17] reported higher fatigue among children with FMF compared to healthy peers. Additionally, they mentioned that children with higher colchicine dosage and older age presented more severe fatigue, while sex or attack frequency had no effect on the level of fatigue. The differences between our studies may be related to preferred PROMs for capturing fatigue. Ozdel et al.[17] employed CIS to evaluate the fatigue, however, the utility of CIS in patients with FMF is unknown as no validation study exists. On the other hand, we demonstrated good to excellent validity and reliability regarding PedsOL-MFS in the present study. Additionally, groups were more heterogeneous in terms of sex distribution and presence of attack frequency in the study by Ozdel et al.[17] compared to the present study. Similar to our results, Duruoz et al.[14] also showed that sex and previous attacks might affect fatigue, and colchicine usage have no impact on fatigue in adult patients with FMF.

Sleep is an important determinant of the quality of life and sleep-related problems are common in children with chronic diseases.[30,31] Poorer sleep quality was reported in children with FMF previously, and sleep disturbances were found to be associated with pain, anxiety, and the number of attacks.[31] The current study was the first to investigate the associations between sleep and fatigue in children with FMF, to the best of our knowledge. Our results suggest that fatigue was associated with poor sleep quality and less sleep duration. Children who were sleeping less than seven hours reported considerably worse fatigue (more than 30%). Thus, evaluating sleep alongside fatigue can help to understand the problems of the patients better.

Pediatric and adult rheumatic diseases are known to lead to an inactive lifestyle.[32-34] Thus, measuring physical activity has become an important part of patient assessment due to the general and disease-related health benefits of physical activity in rheumatic conditions.[35] However, no study has investigated physical activity in children with FMF to date. Results of the previous studies conducted in adult patients with FMF revealed that patients were prone to engage in less physical activity, even during attack-free periods.[36] According to the results of present study, performing less physical activity was significantly associated with higher fatigue levels, and children who had an inactive lifestyle reported higher fatigue. Nonetheless, the direction of this relationship (if the children were inactive due to fatigue or vice versa) is still unknown. As the present study was performed during and recently following Covid-19 period, the pandemic itself and related previous curfews may be other possible factors for limiting physical activity and fatigue eventually.[37] Cardiorespiratory and/or musculoskeletal systems which are essential for fatigue were also reported to be affected by Covid-19 pandemic.[38] Although, none of the participants had Covid-19 during their participation in the study, a previous Covid-19 history was not an exclusion criteria. This could have played a role in self-reported fatigue levels by some children in the present study.

This study has some potential limitations. Only adolescents (aged 13-18 years) were included in the present study. Although the questions are identical in forms for other age groups, fatigue perception in younger children with FMF might be different from adolescents. Thus, our results should be confirmed with other age groups. Drug compliance was inquired verbally in the present study, however, a structured drug compliance assessment might help in interpreting the results more clearly. Besides, the disease activity status was not evaluated thoroughly, and adolescents were considered in attack-free period according to research pediatricians' opinions. Moreover, the number of participants in 'no *M694V* mutation' and 'no colchicine' subgroups were too low to reach a strict conclusion. Future studies with larger sample sizes may be helpful for better understanding the true effect of these variables on fatigue. Evaluating physical activity and sleep-related parameters objectively would also have enhanced our results. Lastly, discriminant validity of PedsQL could not be investigated due to lack of a healthy control group.

PedsQL-MFS is a valid and reliable tool for evaluating fatigue in children with FMF. Being female, recent attacks, physical inactivity, and sleeping less than seven hours seem to be associated with higher fatigue.

Ethical approval

The study was approved by the İzmir Katip Çelebi University, Ethical Committee on 24.06.2021, with number: 0308. All the patients signed informed written consent for publication/participation before the study.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: DCS, DB; data collection: SM, BKD, ÖAG, İİ, İA,

CHK, SK, EP; analysis and interpretation of results: DCS, BKD, ÖAG, DB; draft manuscript preparation: DCS, DB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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