

Development of a medication adherence scale for familial Mediterranean fever (MASIF) in a cohort of Turkish children

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ABSTRACT

Objective. To develop and assess the validity and reliability of an adherence scale concerning medical treatment in paediatric FMF patients.

Methods. The Medication Adherence Scale in FMF Patients (MASIF) is a 18-item questionnaire that evaluates adherence to medication in four domains. Validation of the instrument was accomplished in paediatric FMF patients (aged 2–18 years) under medication at least for 6 months. The first step was to build up the scale through qualitative approach (with interviews using semi-structured questions). Validation analyses included assessment of feasibility, face and content validity; construct validity, internal consistency and test-retest reliability.

Results. One hundred and fifty patients with FMF were enrolled in the study. The mean age of the patients was 11.11 ± 4.02 years and 48.7% of them were male. The MASIF was found to be feasible and valid for both face and content. It correlated with the Morisky Medication Adherence Scale as a gold standard thereby demonstrating good construct validity ($r=0.515$, $p<0.001$). Assessment of content validity identified four subscales. The internal consistency, Cronbach's alpha was 0.728. There was a positive and significant correlation between test and retest scores ($r=0.843$; $p<0.001$). Also, a significant correlation between parents' and children's reports ($r=0.781$, $p<0.001$).

Conclusion. Based on these results, the use of this scale to assess and follow up the adherence to treatment in paediatric FMF patients under medical treatment is recommended.

Introduction

FMF is an autosomal recessive disease characterised by recurrent inflammatory febrile attacks of serosal and synovial membranes along with increased acute-phase reactants. It is the most frequent periodic febrile syndrome and has been proposed as the prototype of the auto-inflammatory disorders (1-5). It is estimated that around 100,000 individuals from the population are at risk for FMF attacks (1). Colchicine is the central component of FMF treatment, since it reduces attack frequency and duration in most patients and it is effective in preventing and arresting amyloidosis, the most dreadful manifestation of FMF (6-8). After the publication of the first reports on the efficiency of colchicine in familial Mediterranean fever (FMF), very few randomised studies have investigated issues related to its long-term use (9). Problems such as colchicine intolerance and colchicine resistance have not been solved yet (10). Another problem that needs to be addressed is the adherence to treatment in FMF (11).

Approximately 10–15% of patients with FMF are defined as non-responders but it was claimed in a study that in fact they are non-compliers (8). The ratio of non-responders to colchicine, which was recorded based on the patients' statements in the first evaluation, was found to be 16% (12). However, the 'true' non-responder ratio was determined as 5% after the correction based on the results of the self-answering question on patient's routine colchicine-consuming habits (8, 13). In this regard, identifying related factors to non-adherence may help in providing approaches.

The reasons for non-adherence include many factors such as complicated treatment plans, the burden of chronic diseases, insufficient communication with the health professionals, insufficient social support, adverse effects of the drugs, or drug interactions (14-17). The adherence of the patient to therapy is as important as the accurate diagnosis or treatment of the disease with accurate timing (18, 19). On the other hand, the current medication adherence scales only measure the adherence to treatment, but not the related factors."

There are a lot of studies on adherence to medication on several diseases such as epilepsy, diabetes, cystic fibrosis and hypertension but not in paediatric rheumatic diseases (20). The consequences of poor adherence are serious and may result in drug resistance, drug reactions, increased morbidity and mortality, and reduced quality of life (21). Poor adherence also affects health care provider behaviour, potentially leading to increased dosages or discontinuation of medication believed to be ineffective (22).

In FMF patients who have been classified as non-responders, data has been reported on the use of different treatments, such as biological agents with significant efficacy (23). However, they have economical cost. Thus, it should be ensured that colchicine treatment was administered adequately before claiming its failure.

Considering the importance of compliance to treatment in FMF, we aimed to develop an adherence scale for medical treatment and assess the validity and reliability in paediatric FMF patients.

Material and methods

Development of the Scale (MASIF)

MASIF was designed by 10 paediatric rheumatologists, 1 paediatric nurse, 1 biostatistician and 1 family physician. Items were derived through: (i) comprehensive reviews of the literature on patient adherence, identifying factors and potential self-report questions (17, 19-22). (ii) semi-structured individual qualitative interviews with 11 patients under medication and their parents. The combination of parameters derived from the literature and from the state-

ments of patients and/or parents was used as study's item pool, which comprised of 31 items. Finally, 17 positive and 14 negative items were included in the item pool. (iii) an expert panel discussion about the relevant factors in FMF medication adherence in the context of their clinical experiences. It is proposed that each of the expert raters on the judging panel responds to the following question for each item: "Is the skill or knowledge measured by this item 'essential' or 'not necessary' to the performance of the construct?" If more than half of the panellists indicate that an item is essential, then the item has at least some content validity. The content validity ratio (CVR) was calculated: $CVR = (n_e - N/2)/(N/2)$, where CVR = content validity ratio, n_e = number of panellists indicating "essential", N = total number of panellists. This Formula yields values ranging from +1 to -1; positive values indicate that at least half the experts (panellists) rated the item as essential.

In light of the expert opinions, 11 items were excluded and thus the eventual scale included 20 items. Accordingly, the content validity was obtained by the members of the group. A pilot test in a convenience sample of 15 patients was performed for face validity to ensure that the questions were clear and understandable to all participants. The acceptability of the survey and the time required to complete the scale were also examined. During the pilot test, the patients were asked to comment on the comprehensibility of the items and whether or not there was a problem in answering the questions. After the pilot test, two items were excluded due to incomprehensible structure. The data obtained from the 15 patients in the pilot test were not included in the data.

As stated above, content validity was established by the members of the group (13 physicians and 1 paediatric nurse with specific experience in the field) with complete agreement. Also 15 patients were asked whether the questionnaire was clear and understandable.

This newly developed form was implicated in the patient group from 19 hospitals with the contribution of 31 au-

thors, and validity/reliability analyses were performed. Activities in this step were detailed in the following sections. The final 18-item scale is presented in Appendix A. Items were grouped into 4 categories: knowledge about the medication, adherence to the treatment, barriers to drug use, factors that may increase compliance. The participants answered each item on a Likert scale (1 = strongly agree, 2 = agree, 3 = no idea, 4 = disagree, 5 = strongly disagree). The total score ranged from 18 to 90.

In step 4, each participant also completed a previously validated questionnaire: Morisky medication adherence scale.

Morisky Medication Adherence Scale: The Morisky medication adherence scale was developed to assess the extent to which patients took their prescribed medications (24). The theory underlying the scale was that medication non-adherence could be caused by forgetting, carelessness, stopping the drug when feeling better and/or stopping the drug when feeling worse. As such, the scale assessed both unintentional non-adherence (forgetting and carelessness) and intentional non-adherence (stopping the drug when feeling better/worse) with dichotomous responses ('yes' and 'no'). The structure of the questions was reversed to avoid the 'yes-saying' bias. Each patient had a scale score ranging from 0 to 8, and higher scores indicated better medication adherence. This scale was used as a gold standard in order to evaluate the criterion validity of MASIF.

Patient population

All FMF patients (aged between 2-18 years and under oral medication for at least 6 months) who had been seen in the 19 study centres between April 2012 and July 2013 were enrolled. Their parents/guardians gave informed consent to participate. Patients with another disease that required regular drug use were excluded.

The questionnaire was completed only by the parents if the patient was younger than 7 years old. For patients older than 7 years, they and their parents were both included in the interview. The study was approved by the local ethics committee of the research hospital.

Questionnaire completion

Prior to the study visit, a parent (the mother, whenever possible) or legal guardian of each patient was asked to complete the Turkish parent version of the MASIF and Morisky adherence scale. The two questionnaires were presented to the raters in random order. The child (if aged more than 7 years) was also asked to complete the Turkish patient version of the MASIF and Morisky adherence scale with his parent (25). A researcher assisted parents and children if they had questions during questionnaire completion.

Clinical assessments

At the time of the study visit, the following data were obtained from each patient/parent: sex, age at disease onset, disease duration, attack patterns and age at study visit. The attending paediatric rheumatologist rated the physician's global assessment of overall disease activity on a 10-cm visual analogue scale (VAS; 0: no activity, 10: maximum activity) and also noted the therapies from disease onset and treatment decision. Laboratory parameters included erythrocyte sedimentation rate (ESR) and C-reactive protein level (CRP).

Validation procedures

To validate the MASIF, the Outcome Measures in Rheumatology Clinical Trials (OMERACT) filter for outcome measures in rheumatology was applied (26, 27). Feasibility or practicality of the MASIF was determined by addressing the issues of brevity, simplicity, and easy scoring, and from the percentage of missing values. The time needed to complete the MASIF was also assessed. Face and content validity of the MASIF were discussed in the development steps of the scale.

Criterion validity is a measure of the extent to which values on an instrument agree with those of a gold standard. The Morisky Adherence Scale was accepted as the gold standard for evaluation of the criterion validity.

A correlation coefficient was calculated between the total scores obtained in the MASIF scale and the Morisky scale. The criterion of assuring the criterion validity of MASIF was taken as a mini-

No Items

1	I know about my illness and I am aware that my treatment will continue for a long time.
2	I sometimes forget to take my medication.
3	I rely on the treatment prescribed for my disease.
4	I refrain from others when taking drugs
5	Continuous drug usage affects my daily life.
6	When I am out of home (on vacations, travels, etc.) I forget to take my drugs.
7	I wish this disease had a treatment without drugs.
8	I sometimes do not take my drugs on time because of my daily routine.
9	I think my illness will get better, if I use my drug regularly.
10	I know the adverse effects of the drug.
11	I need to be convinced to use my medication regularly, for a long time.
12	I'm afraid that continuous drug use may lead to other diseases.
13	If I leave my drug, my disease may worsen.
14	I could not get used to using my drug regularly.
15	When I realise that I forgot to take my medication, I take my drug even it is delayed, I do not skip doses.
16	When I disrupt my drug my complaints may increase.
17	I am tired of continuous drug use.
18	I think it is quite difficult to use medicine in multiple doses during a day.

mum value of 0.30, calculated from the correlation coefficient (28, 29). As criterion validity, the correlation coefficients were calculated between the total scores obtained from the MASIF and Morisky Adherence Scale.

Construct validity is a form of validation that examines whether the construct in question, in this case the MASIF, is related to other measures in a manner consistent with a prior prediction. The "Principal Components Analysis" among the "descriptive factor analysis" was used to determine the titles of the scale items (28, 30). Prior to the factor analysis, the Kaiser-Meyer-Olkin (KMO) test was used to evaluate the sufficiency of the sample size for the factor analysis. A KMO value of >0.60 was accepted as an indicator of a sufficient sample size for the factor analysis. For interpretation of the factor analysis outcomes, particular attention was paid to the factor loadings to be at least 0.30 (28-31). Finally, the factors observed were named according to the items included.

Reliability; the internal consistency and test-retest reliability were evaluated (25). **Internal consistency:** A Cronbach's alpha internal consistency coefficient was calculated. The Cronbach's alpha coefficient values for the scale that were

≥0.70 were accepted as a criterion of internal consistency (25, 28, 32).

Test-retest reliability: Test-retest was implemented to 29 patients after 10-20 days from the first implementation of the scale. The statistical significance of the difference between the mean values of the total scores obtained in the test and the retest of the scale was primarily analysed using the "Paired Sample Test". Second, the correlation between the test and retest scores was analysed in order to determine the consistency between the two calculations, and a "consistency coefficient" was calculated (28, 33).

Both parents and children were asked to complete the scale and the correlation between parents' reports and children's reports was evaluated.

A scale instruction was prepared for the individuals who are going to use the scale. It describes the appropriate subjects, the scoring and the interpretation procedures.

Statistics

Descriptive data are expressed as numbers and percentages for the numerical variables, and as mean ± standard deviation (SD) for the measurement variables. Pearson's correlation coefficient was calculated for the "correla-

Table I. Characteristics of the participants.

Characteristics		
Age (Mean±SD)	11.21 ± 4.05	
Age at the time of diagnosis (Mean±SD)	7.51 ± 4.10	
Time duration after the diagnosis (Mean±SD)	3.70 ± 2.72	
Number of attacks in a year (Median±SD)	11.00±10.74 (min. 0 - max 52)	
Duration of an attack (hour) (Median±SD)	48.00±34.82 (min. 0 - max 240)	
Gender	n	%
Male	73	48.7
Female	77	51.3
<i>Family history of FMF</i>		
Yes	81	54.0
No	57	38.0
Unknown	12	8.0
<i>Pattern of attacks</i>		
Regular	48	32.0
Irregular	91	60.7
Unknown	11	7.3
<i>Colchicine doses</i>		
1 mg/24 h	76	50.7
1.5 mg/24 h	43	28.7
2 mg/24 h	25	16.7
>2 mg/24 h	2	1.3
Unknown	4	2.7

SD: Standard deviation; FMF: Familial Mediterranean Fever.

Table II. The results of item analyses.

	Item	Scale Mean Score If Item Deleted	Scale Variance if Item Deleted	Corrected Item/Total Correlation	Cronbach's Alfa If Item Deleted
n:150	Item 1	57.70	70.05	0.175	0.706
	Item 2	58.75	61.75	0.444	0.702
	Item 3	57.74	69.29	0.256	0.722
	Item 4	59.61	60.98	0.479	0.698
	Item 5	59.16	62.27	0.440	0.703
	Item 6*	66.22	73.79	-0.150	0.708
	Item 7	59.22	63.00	0.316	0.717
	Item 8	60.75	69.62	0.128	0.730
	Item 9	59.31	61.88	0.376	0.710
	Item 10	57.94	68.06	0.293	0.719
Item number: 18	Item 11	58.64	68.55	0.132	0.733
	Item 12	58.91	61.73	0.481	0.699
	Item 13	59.58	66.34	0.214	0.726
Cronbach's alpha: 0.728	Item 14	58.08	69.84	0.156	0.727
	Item 15	58.75	61.21	0.437	0.703
	Item 16	58.13	64.83	0.396	0.709
	Item 17	58.25	70.60	0.044	0.738
	Item 18	59.91	64.14	0.345	0.713
	Item 19*	66.80	70.89	-0.017	0.706
	Item 20	60.16	65.11	0.300	0.717

*Items 6 and 19 were excluded from the scale after item analyses.

tion-based item analysis". Cronbach's alpha value was calculated for the reliability analyses of the scale. "Paired Sample Test" and the correlation coefficient were calculated in the test-retest analyses, performed for evaluation of the reliability. CVR (Content Validity

Ratio) and CVI (Content Validity Index) were calculated for the content validity. Pearson's correlation coefficient was used for the criterion validity. The Principal Components Analysis among the descriptive factor analyses was used for evaluation of construct va-

lidity and the "Equamax Rotation" was performed. The Kaiser-Meyer-Olkin (KMO) test was used prior to the factor analysis. SPSS package program for windows v.15.0 (SPSS Inc. Chicago, IL, USA) was used. $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

None of the parents/guardians of eligible patients seen in the study period refused participation and no subject was excluded for other reasons. Overall, 150 patients were enrolled in the study (Table I).

Feasibility and face and content validity

Mean time for completing the MASIF was 3.4 minutes (range 2–6) for parents, and 5.3 minutes (range 3–10) for children. There were no missing responses. Face and content validity are discussed above.

Criterion validity

As criterion validity, the correlation coefficients were calculated between the total scores obtained from the MASIF and Morisky Adherence Scale. There was a significant correlation between MASIF scores and Morisky scores ($r = -0.515$, $p = 0.000$).

Construct validity

According to the factor analysis, a total of four factors were gathered, accounting for 58% of the total variance and having an eigenvalue of greater than 1 that could come together meaningfully. The factors were named considering the items gathered under which were examined with regard to their content. The first factor was named "knowledge about the medication" (1st, 10th, 13rd and 16th items); the second factor was named "adherence to the treatment" (2nd, 5th, 6th, 8th, 15th and 17th items), the third factor was named "barriers to drug use" (4th, 7th, 12th, 14th and the 18th items) and the fourth factor was named "the factors that may increase adherence" (3rd, 9th and 11th items).

The Kaiser-Meyer-Olkin (KMO) value was found to be 0.652 with a Barlett test outcome of 706.294 and a p -value

of <0.01 . The results of item analyses are presented in Table II. Among the 58% variance that had been accounted for, 14% were explained by the first factor, 12% were explained by the second factor, 12% were explained by the third factor and 10% were explained by the fourth factor.

According to our scale, a high score showed a good adherence to treatment. The cut-off point was determined as 60 points. A point over 60 was accepted as "good medication adherence" and a point less than 60 was considered as "bad medication adherence" (Table III). The ROC curve is shown in Figure 1.

Internal consistency

The Cronbach's alpha coefficient calculated for the 18 items subsequent to the item analysis was 0.728. The cronbach's alpha values of the items are shown in Table II.

Test-retest reliability

The mean values of total scores obtained in the first test and the retest on 29 participants were 61.51 ± 8.70 and 60.65 ± 8.29 , respectively ($t=0.971$; $p=0.340$). The correlation analysis (test-retest reliability) showed a highly significant positive correlation ($r=0.843$; $p<0.001$).

Both the parents and the child (if aged more than 7 years) completed the questionnaire. The correlation between parents' reports and children's reports was evaluated and it was found a significant correlation between them ($r=0.781$, $p<0.001$).

Discussion

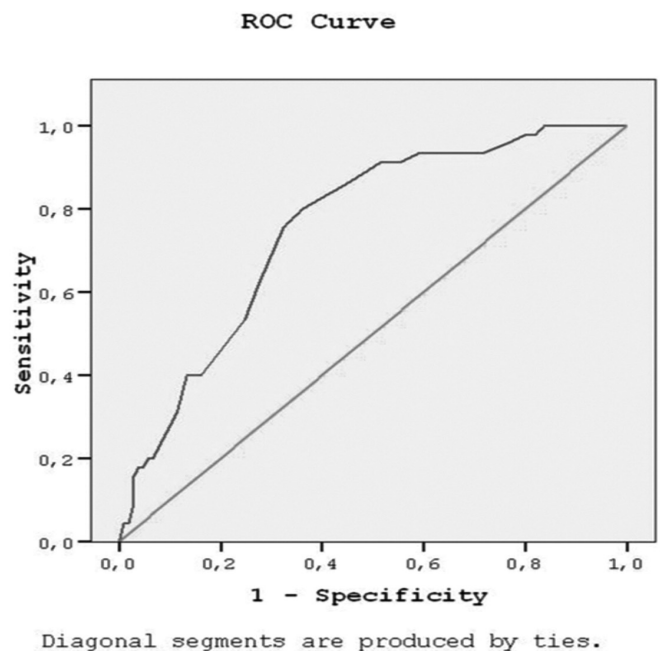
In this study, we have described the development of a new measure of medication adherence for children with FMF. It is short, simple, and quickly applied (taking only 3–4 minutes to complete and score) and therefore seems to be practical for use in standard clinical care. The instrument was found to be feasible and to possess face and content validity, criterion validity, construct validity and good reliability in patients with FMF. By documenting these key measurement properties, we have demonstrated that the MASIF is a valid tool for the assessment of medi-

Table III. Possible cut-off points of MASIF.

MASIF Cut-off points		Morisky		Sensitivity %	Selectivity %	PPV* %	NPV** %
		Bad adherence (n)	Good adherence (n)				
55	Bad adherence	25	2	23.8	95.6	92.6	35.0
	Good adherence	80	43				
60	Bad adherence	51	4	48.6	91.1	92.7	43.2
	Good adherence	54	41				
65	Bad adherence	79	21	75.2	53.3	79	48
	Good adherence	26	24				
70	Bad adherence	96	34	91.4	24.4	73.8	55
	Good adherence	9	11				

*Positive predictive value. **Negative predictive value.

Fig. 1. The ROC curve.



cation adherence in this patient population for oral drugs and is, therefore, potentially applicable in both clinical and research settings.

Colchicine has been described as the best treatment option for both reducing attacks and preventing the development of amyloidosis if used regularly and in adequate doses. Colchicine resistant patients are in fact thought to be non-compliers rather than being non-responders due to non-adherence to divided daily dosing regimens. This problem causes inadequate intake of the drug and eventually increases the risk of amyloidosis development which is the most deadly complication of the disease. Considering all these facts, ad-

herence to treatment is paramount and needs to be monitored in FMF.

Evaluation of its validity determines whether a scale is proper for the stated property or not. In this study, the content validity was investigated in order to determine whether the items of MASIF represented the field desired to be measured or not (28, 29, 31). At the end of the content and face validity analyses performed for the starting scale with 31 items, 11 items were eliminated and the validities were consequently provided. Analysis pertaining to the criterion validity revealed a significant positive correlation between the MASIF and the Morisky scores. We evaluated criterion validity by using Morisky scale because

there is no test measuring colchicine level in the blood. So we can not evaluate adherence to colchicine treatment. For example; HgA1C can be used as a gold standard in diabetes. However there is not any parameter or test to use as a gold standard in FMF (34, 35). Herewith, although Morisky Scale may be used to evaluate adherence to treatment, it does not show what the exact problem of non-adherence is *e.g.* forgetting to take the drug, not taking the drug because of the adverse events, etc. On the other hand, MASIF evaluates not only the drug adherence but also determines the underlying cause. Yet, it includes four subdimensions (“knowledge about medication”; “adherence to treatment”, “barriers to drug use” and “factors that may increase adherence”). A correlation coefficient of >0.30 between MASIF and Morisky was an indicator of a valid criterion analysis. The factor analysis method was used for evaluation of the construct validity of the scale. In the factor analysis performed for evaluation of the construct validity of MASIF, 4 factors have been defined (Table III). These obtained values showed that the scale had a successful factor construction (28-31). The scale does not only focus on the non-adherence but aids to determine the contributing factors (knowledge deficit of the disease, general considerations about the situations). In addition to the numerical variables, gathering of the items together to form a meaningful whole is an important issue in the evaluation and interpretation of factor analysis outcomes (31, 36-38). Following the determination of a proper factor construction for the scale, the factors that had arisen were indicated. The MASIF is able to collect the data on time, shows no variation in time, and that it can be repeated (25, 28, 29). The Cronbach’s alpha coefficient was found to be 0.728 and this value was an indicator of the reliability of MASIF. The test/retest reliability analyses also demonstrated that MASIF yielded consistent outcomes and ensured the test-retest reliability. Also the significant correlation between parents’ reports and children’s reports was an indicator of reliability. Our study should be viewed in light of

certain limitations. Although we present the English translation of the questionnaire (Appendix A), the instrument was validated in Turkish patients. It is possible that children and their parents elsewhere might respond differently to the MASIF questionnaire due to cultural and language differences. In closing, we have developed a new short and simple measure for the assessment of medication adherence in patients with FMF. We recommend using it in standard clinical care and clinical trials. The MASIF is proposed for use as both proxy report and patient self-report (if aged 7–18 years). This instrument, which was validated in its Turkish version, should be further tested in different patient groups and cultures. Furthermore, we suggest that adjustment studies of this scale for adult patients with FMF and for other chronic rheumatic diseases (requiring oral drug use) are conducted.

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