Factors associated with damage in patients with familial Mediterranean fever

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ABSTRACT

Objective. *Defining predictors of damage would improve patient care. We applied damage indexes to patients with familial Mediterranean fever (FMF) and identified the predictors of damage.*

Methods. *This is a cross-sectional analysis of 926 FMF patients, who fulfilled the Tel-Hashomer criteria and had at least six months of follow-up. Patients were stratified according to their damage status (damage vs. no damage) defined with autoinflammatory disease damage index (ADDI) and modified ADDI (excluding musculoskeletal pain). We used logistic regression analysis to investigate independent predictors of damage for both indexes.*

Results. *Mean disease duration was 21.6±11.9 years. 527 patients (57%) had damage according to ADDI. Median ADDI score was 1 (0-11). Most common FMF-related damages were observed in musculoskeletal, reproductive and kidney domains. Female gender, inflammatory comorbidity, colchicine resistance, colchicine non-adherence, musculoskeletal attack dominance, diagnostic delay, follow-up time, and smoking history remained independent predictors of damage according to ADDI score. The rate of patients with damage defined by modified ADDI was only to 23%. M694V/M694V homozygosity, female gender, musculoskeletal attack dominance, colchicine resistance, persistent inflammation, follow up time and family history of amyloidosis were found to be predictors of damage according to modified ADDI score.*

Conclusion. *Our study is the first to apply comprehensive damage indexes to FMF patients and identified predictors of damage. Factors linked to a severe FMF phenotype, including M694V homozygosity and persistent inflammation, were associated with only modified ADDI. Our findings justify the concerns about musculoskeletal pain and might point to the need for re-evaluation of ADDI for FMF patients.*

Introduction

Familial Mediterranean fever (FMF) is the most common systemic autoinflammatory disease characterised by recurrent, self-limiting attacks of fever, serositis, and musculoskeletal manifestations (1). FMF is most prevalent in individuals with Mediterranean ancestry, especially Turks, Arabs, non-Ashkenazi Jews, and Armenians (2). FMF is an autosomal recessively inherited disease with incomplete penetrance caused by mutations in the *Mediterranean fever* (*MEFV*) gene that encodes the pyrin protein, which has critical roles in the regulation of inflammatory pathways (3, 4). Mutations in exon 10 of the *MEFV* gene result in clinical manifestations of the disease, largely due to interleukin (IL)-1β overproduction (5, 6)

Chronic, even recurrent episodes of inflammation can cause damage in nearly all organ systems (7). Given the disease prevalence, FMF is the most studied autoinflammatory disease and is associated with renal (8, 9), reproductive (10, 11), musculoskeletal (12-15), and gastrointestinal damage (16). Managing FMF is aimed at decreasing attack frequency and preventing organ damage (17). Some breakthrough target therapies for FMF have become available with blocking IL-1β signalling (17). The drugs used in these therapies are effective in controlling inflammation and disease manifestations. However, the efficacy of these drugs to prevent damage is not yet known; indeed, there was no available validated damage index until very recently.

Comprehensive assessment of damage is crucial for guiding physicians in monitoring patients and unifying outcome measures in therapeutic studies. To fulfill these unmet needs, the Autoinflammatory Disease Damage Index (ADDI) was developed. The ADDI comprises 18 items grouped into 8 categories. Scholars have expressed reservations about one of the items, musculoskeletal pain, which was nearly excluded from the ADDI during both the development and validation phases (18, 19).

Defining predictors for damage improves patient care. Available studies on FMF-related damage have focused on individual damage domains (7-15). This study is the first to analyse cumulative damage in FMF patients and to apply comprehensive damage indexes to FMF. We identified the frequency of each damage item and analysed the association between patients' characteristics and damage, and we identified the independent predictors of damage.

Methods

Familial Mediterranean fever in Central Anatolia (FiCA)

The FiCA cohort is multicentre-accessible, duplication-disabled, and web-based. We recruited 971 adult Turkish FMF patients between January and December 2018, who were followed at the outpatient rheumatology clinics of three different university hospitals located in the Central Anatolia region of Turkey. All participants were above 18 years of age and had a definitive diagnosis of FMF according to the Tel Hashomer criteria (20). The FiCA cohort was approved by the local ethics committees of each centre. All patients gave written informed consent to participate. This cross-sectional analysis was based on cohort data of 926 patients who had been diagnosed with FMF for 6 months or more.

Demographic data, FMF disease characteristics, attack types (ever experienced), comorbid conditions, treatment modalities, and disease complications were thoroughly investigated. A comprehensive laboratory assessment including the complete blood count, erythrocyte sedimentation rate, C-reactive protein level, urine protein/creatinine ratio, and liver and renal function tests was done for each patient during attack-free periods. Genotype data (if available) were recruited from computer-based patient files. M694V, M694I, M680I, V726A, R761H, E148Q, and A744S were considered pathogenic variants associated with FMF (21). Patients were designated as mutation negative if any of the aforementioned genes were absent. Disease severity was assessed by the International Severity Score for FMF (ISSF) at the enrollment visits (22). Colchicine adherence was assessed with standardised questions during face-to-face interviews. Colchicine resistance was defined as experiencing one or more attacks per month despite the regular use of the maximally tolerated dose of colchicine for at least six months (17). Persistent inflammation was defined as increased C-reactive protein (CRP) levels (mg/L) measured during attack-free periods (≥2 weeks without an attack) and was evident in ≥75% of measurements at all follow-up visits while not using targeted biologic therapies. Amyloidosis was confirmed from patients' pathology records. The elapsed time between the age at diagnosis and that at disease onset was defined as the diagnostic delay, while the time between each patient's current age and their age at diagnosis was defined as the follow-up time. Accompanying inflammatory diseases, including spondyloarthropathies, inflammatory bowel diseases, skin diseases, and other inflammatory arthritis, were carefully evaluated, and data on inflammatory diseases were derived from patient interviews and hospital records. All current and past inflammatory comorbidities were considered, and all interviewed diseases were confirmed with patient health records.

Assessment of damage, the ADDI, and the modified ADDI

The ADDI was developed using a Delphi consensus process (18, 19). The ADDI has convergent and discriminant validity with good inter-rater reliability (18). As mentioned above, the ADDI comprises 18 items (sub/infertility, amenorrhea, amyloidosis, proteinuria, renal insufficiency, growth failure, pubertal delay, developmental delay, serosal scarring, cognitive impairment, elevated intracranial pressure, central nervous system involvement, hearing loss, ocular involvement, joint restriction, bone deformity, osteoporosis, and musculoskeletal pain), which are grouped into 8 categories (reproductive, renal/amyloidosis, developmental, serosal, neurological, auditory, ocular, and musculoskeletal damage) (18). Persistent and irreversible changes in these domains that developed after the onset of disease and were present for over six months were defined as damage (18). However, as noted earlier, musculoskeletal pain has been a controversial item in the ADDI from its developmental phase, largely because the assessment of musculoskeletal pain is subjective. Considering the concerns about musculoskeletal pain item (18, 19), we defined modified ADDI, which excludes musculoskeletal pain from the ADDI. All patients were evaluated meticulously regarding each damage item in the ADDI and modified ADDI. The presence of a damage item was determined using existing hospital records and further evaluation of the suspected condition during patient interviews and physical examinations. Osteoporosis screening was applied to patients considered to be at risk. Infertility was defined as the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse, not due to known disorders in the unaffected partner. Additional tests specified in the glossary of terms of the ADDI were performed in suspected patients. Not all patients were subjected to cognitive evaluations or hearing testing.

The ADDI was developed as a quantitative measure of cumulative organ damage. However, we used it as a categorical variable and stratified patients according to their damage status (present or absent) defined by the ADDI and modified ADDI. We separately analysed the predictors of damage for each index.

Statistical analysis

All statistical analyses were performed using SPSS software (v. 15.0 for Windows; SPSS Inc., Chicago, IL, USA).

The variables were investigated using visual (histograms and probability plots) and analytical (the Kolmogorov-Smirnov and Shapiro-Wilk tests) methods to determine the distribution of data. The chi-square test for categorical variables, the Wilcoxon rank sum test, and the independent samples T-test for continuous variables (where appropriate) were used to determine whether there was a significant difference between the characteristics of patients grouped according to damage status.

For the multivariable analysis, first, we assessed the relationship between each variable and the damage. Variables that had a significant association with damage ($p<0.1$) were then entered into a multivariable model, and those that remained significant were retained in the final model. The ISSF was not included in the multivariable model due to collinearity with other independent variables, including similar domains within both damage indexes. Hosmer-Lemeshow goodness-of-fit statistics were used to assess model fit. A 5% type I error level was used to infer statistical significance.

Results

Table I details the characteristics of patients stratified according to damage status, as defined by the ADDI. Of the patients, 527 (57%) had damage according to this index. The mean disease duration at the time of recruitment was 21.6±11.9 years. Damage was found more frequently in female patients, in patients with a smoking history (current or past), and in those who were less educated. The diagnostic delay and follow-up time were longer in the damage-positive group. M694V homozygous mutation, inflammatory comorbidities, arthritis, erysipelas-like erythema, exertional leg pain, colchicine resistance, colchicine non-adherence, and persistent inflammation were more common in patients with damage, while peritonitis was more common in patients with no damage. Age at disease onset, visit adherence, family history, family history of amyloidosis, mutations excluding homozygous M694V, fever, and pleuritis were comparable between the groups. Patients with damage had

Table I. Clinical and demographic characteristics of the patients in the FICA cohort.

	Any Damage n=527	No Damage n=399	*p*-value
Sex, female	337 (64%)	229 (57%)	0.048
Age at disease onset, years			0.12
≤18	407 (77%)	290 (73%)	
>18	120 (23%)	109 (27%)	
Mean (SD)	13.7 (10.8)	14.2 (10.1)	0.74
Age at diagnosis, years			
Mean (SD)	25.7 (13.7)	23.4 (12.4)	0.008
History of smoking, ever	241 (46%)	157 (39%)	0.05
Years in education			<0.001
<11	186 (35%)	90 (22%)	
11-15	173 (33%)	147 (37%)	
15≤	168 (32%)	162 (41%)	
Visit adherence	352 (66.8%)	284 (71.2%)	0.282
Diagnosis delay, years			0.004
≤10	302 (57.3%)	266 (66.7%)	
>10	225 (42.7%)	133 (33.3%)	
Mean (SD)	11.9 (11.4)	9.2 (10.3)	<0.001
Follow-up time, years			0.02
≤10	277 (53%)	240 (60%)	
>10	250 (47%)	159 (40%)	
Mean (SD)	11.4 (8.2)	10.2 (7.6)	0.01
Mutations*[¥1]			0.09
M694V/M694V	140 (26.6%)	75 (18.8%)	
M694V/M680I	42 (8%)	32 (8%)	
M680I/M680I	11 (2.1%)	11 (2.8%)	
M694V/any	170 (32.3%)	135 (33.8%)	
M680I/any	30 (5.7%)	23 (5.8%)	
Mutation negative	24 (4.6%)	22 (5.5%)	
Others	40 (7.6%)	25 (6.4)	
M694V/M694V homozygous	140 (26.6%)	75 (18.8%)	0.022
Inflammatory comorbidity	143 (27.1%)	50 (12.5%)	<0.001
Fever	443 (84.1%)	328 (82.2%)	0.42
Peritonitis	474 (89.9%)	374 (93.7%)	0.05
Pleuritis	260 (49.3%)	175 (43.9)	0.12
Arthritis	268 (50.9%)	126 (31.6%)	<0.001
ELE	155 (29.6%)	83 (21%)	0.003
Exertional leg pain	135 (25.9%)	60 (15.2%)	<0.001
Dominant attack type[¥1]			<0.001
Serositis	360 (74.5%)	355 (90.3%)	
Musculoskeletal	123 (25.5%)	38 (9.7%)	
Attack frequency, last year	5.45 (7.4)	3.2 (4.8)	<0.001
Colchicine resistance	63 (12%)	13 (3.3%)	<0.001
Additional treatment			<0.001
Anti-IL-1	63 (12%)	19 (4.8%)	
Anti-TNF	30 (5.7%)	7 (1.8)	
Family history of FMF[¥2]	209 (41.6)	152 (40.2%)	0.69
Family history of amyloidosis[¥2]	35 (6.6%)	18 (4.5%)	0.15
Colchicine adherence			0.006
Adherent	386 (73.2%)	286 (71.7%)	
Partial	93 (17.6%)	92 (23.1%)	
Nonadherent	41 (7.8%)	14 (3.5%)	
Persistent inflammation	99 (18.8%)	43 (10.8%)	0.001
ISSF			<0.001
Mild	183 (34.7%)	266 (66.7%)	
Intermediate	286 (54.3%)	130 (32.6%)	
Severe	58 (11%)	3 (0.8%)	
Median score (min-max)	3 (0-9)	2 (0-6)	<0.001

*MEFV gene mutations were available for 780 patients; [¥1]50 patient had them both. [¥2]Missing data=45.

Table II. Frequency of each damage item listed in ADDI index.

Infertility/subfertility	64 (11%)
Amenorrhea[¥1]	35 (4%)
Amyloidosis	55 (5.9%)
Proteinuria[¥2]	64 (7.3%)
Renal insufficiency	35 (3.8%)
Growth failure	10 (1.1%)
Puberty delay	14 (1.5%)
Serosal scarring[¥3]	17 (2.2%)
Joint restriction	27 (2.9%)
Osteoporosis[¥4]	25 (3.3%)
Musculoskeletal pain	448 (48.4%)
ADDI score, median (min-max)	1 (0-11)

*582 patients were eligible for analysis (who had been willing to have children); ¥ missing (unknown) data; [¥1]42, [¥2]52, [¥3]139, and [¥4]163.

more musculoskeletal than serositis-type attacks compared to patients with no damage.

The rate of patients with damage declined to 23% when damage was defined by the modified ADDI. Similar differences among patient characteristics were detected when the stratification was dependent on defining damage by the modified ADDI (data not shown).

Frequency of damage items

In Table II, the frequency of patients with each damage item of the ADDI is presented. The median ADDI score was 1 (min. 0–max. 11). The most common domains of FMF-related damage were musculoskeletal, reproductive, and kidney. Of the patients, chronic musculoskeletal pain was present in 48%, joint restriction in 2.9%, infertility/subfertility in 11%, amenorrhea in 4%, proteinuria in 7.3%, amyloidosis in 5.9%, and renal failure in 3.8%.

Predictors of the ADDI and modified ADDI

Table III shows the baseline characteristics of patients that were associated with damage according to the ADDI and modified ADDI in multivariable logistic regression models. In the final multivariable model, the female gender, inflammatory comorbidity, colchicine resistance, colchicine non-adherence, musculoskeletal attack dominance, diagnostic delay, follow-up time, and smoking history remained independent predictors of damage based on the ADDI.

Table III. Predictors of ADDI and Modified ADDI.

	ADDI Multivariable		Modified ADDI Multivariable	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Sex				
Female	1.55 1.1-2.2)	0.02	1.72 (1.14-2.59)	0.010
Male	Ref		Ref	
History of smoking				
Never	Ref		-	
Ever	1.43 (1-2.05)	0.05	-	
Education, years				
<11	Ref		Ref	
11≤	0.71 (0.51-0.99)	0.04	0.61 (0.40-0.93)	0.02
Diagnosis delay, years				
≤10	Ref		-	
>10	1.78 (1.26-2.5)	0.001	-	
Follow up time, years				
≤10	Ref		Ref	
>10	1.53 (1.1-2.14)	0.014	1.86 (1.26-2.75)	0.002
M694V/M694V homozygous				
Absent	-		Ref	
Present	-		1.63 (1.06-2.51)	0.03
Inflammatory comorbidity				
Absent	Ref		-	
Present	2.0 (1.3-3.1)	0.02	-	
Colchicine resistance				
Absent	Ref		Ref	
Present	2.63 (1.25-5.57)	0.011	2.29 (1.17-4.54)	0.016
Colchicine adherence				
Non adherent	2.43 (1.19-4.94)	0.015	-	
Adherent	Ref		-	
Dominant attack type				
Musculoskeletal	2.74 (1.77-4.34)	<0.001	1.62 (1.02-2.57)	0.04
Serositis	Ref		Ref	
Family history of amyloidosis				
Absent	-		Ref	
Present	-		2.50 (1.25-5.0)	0.010
Persistent inflammation				
Absent	-		Ref	
Present	-		1.82 (1.06-3.15)	0.03

Whole co-variates except disease onset and family history of FMF were presented in the table. There was no significant association between any dependent variable, disease onset and family history of FMF.

Harbouring M694V/M694V homozygous mutation, the female gender, musculoskeletal attack dominance, colchicine resistance, persistent inflammation, longer follow-up time, and a family history of amyloidosis were found to be associated with a high risk of damage according to the modified ADDI. Having more than 11 years of education was inversely associated with damage according to both the ADDI and modified ADDI.

Discussion

Well-developed damage assessment instruments can be used as outcome measures to guide patient management. Defining accumulated damage and risk factors for damage is important for stratification in both clinical trials and disease management. Current knowledge focuses on damage items separately, and a comprehensive assessment of damage and predictors of damage accrual are largely lacking. To the best of our knowledge, this is the first study that applied damage indexes to a large sample of FMF patients in a real-life setting. We identified the frequency of each damage item, as well as clinical determinants of damage, according to both the ADDI and modified ADDI.

Fifty-seven percent of patients (527 patients) had at least one damage item according to the ADDI. Median ADDI score was 1 (min 0 - max 11). The most common FMF-related damage items

were observed in the musculoskeletal, reproductive, and kidney domains. As noted above, the female gender, inflammatory comorbidity, colchicine resistance, colchicine non-adherence, musculoskeletal attack dominance, diagnostic delay, follow-up time, and smoking history were found to be independent predictors of damage according to the ADDI. The modified ADDI revealed 216 patients (23%) with damage, and based on this index, we identified M694V homozygosity, the female gender, musculoskeletal attack dominance, colchicine resistance, persistent inflammation, longer follow-up time, and a family history of amyloidosis as predictors of damage. This is noteworthy because factors linked to a severe FMF phenotype were revealed to be predictors only of the modified ADDI score. Both M694V homozygous mutation and persistent inflammation are well-established determinants of severe disease and are associated with an increased risk of individual damage items (23-25). M694V homozygosity constitutes a risk for early-onset disease (9), severe disease phenotypes (9, 23), and increased incidence of amyloidosis (26, 27). Similarly, persistent inflammation is associated with growth retardation (28), amyloidosis (29, 30), anemia (31), decreased bone density (32), and infertility (11, 24). A damage assessment instrument with good construct validity should reflect disease severity and risk factors. However, we could not identify either as a predictor of damage using the ADDI. On the one hand, these results might have been caused by sampling variability, which is unlikely since our multicentre cohort comprised FMF patients from a real-life setting with no exclusion criteria besides follow-up time (>6 months). On the other hand, this result might validate concerns about the reliability of the musculoskeletal pain item in the ADDI.

Nearly half of the patients (48.4%) had musculoskeletal pain, and it was the only damage item in 34% of the patients. As a damage item, musculoskeletal pain was defined as non-inflammatory musculoskeletal pain that impaired the activities of daily living (18), was weighted the same as amenorrhea and proteinuria (18). Not only is musculoskeletal pain nonspecific, subjective by definition, and lacking in causality and permanency, but it is also difficult to assess due to its association with ongoing disease activity (33). Of note, arthritis, exertional leg pain, and musculoskeletal-dominant attacks were more frequent in the damage-positive group. These are all parameters of disease activity that can be misleading for patients to report musculoskeletal pain as damage. Several other clues exist in this regard. Inflammatory comorbidities and smoking were identified as independent predictors only of the ADDI score. Smoking contributes to peripheral vascular disease and may cause chronic musculoskeletal pain (34), as do inflammatory comorbidities (35). Furthermore, researchers have found that smoking may increase pain sensitivity in general and aggravate localised and generalised pain, including joint and musculoskeletal pain (36).

The main purpose of a damage index is to quantify damage objectively and reliably to allow intra- and inter-individual comparisons. Considering the prevalence, association with active disease, non-causality, and impact on the total scores and predictors of the ADDI, our findings imply that musculoskeletal pain contradicts this purpose. Therefore, we used another multivariable model in order to determine whether musculoskeletal pain was a predictor of the damage according to modified ADDI score (data not shown) and we found as it was. All the covariates from the first model, except for musculoskeletal attack dominance, remained as predictors in the new model. Musculoskeletal pain is one of the major characteristics of diseases that limit daily physical activities, and it has a significant impact on patient-reported outcomes. However, no other damage index (*e.g.*, the Vasculitis Damage Index (37) or the SLICC/ACR damage index (38)) includes an item as subjective as musculoskeletal pain. Therefore, rather than a damage item, it would be better to characterise musculoskeletal pain as a risk factor, which might still draw attention toward better management.

Our results have also highlighted the importance of persistent inflammation and colchicine resistance. The proportion of persistent inflammation in patients with damage was almost twice as much as in those without. Persistent inflammation was found to be an independent predictor only of the modified ADDI score. Therefore, it should be kept in mind that laboratory follow-ups are an important tool in making decisions regarding escalation of therapy, even without complaints. It is not surprising that factors associated with disease severity, such as higher attack frequency, a tendency toward colchicine resistance, and, as a result, the need for additional treatment, were more frequent in patients with damage. Among these, only colchicine resistance was found to be independently associated with both ADDI and modified ADDI scores. IL-1β antagonists, which suppress both disease activity and inflammation, made a breakthrough in management of FMF patients (39, 40). Hence, although longitudinal studies are needed, the use of these agents in cases of persistent inflammation or colchicine resistance might prevent future damage, as these might be reversible risk factors of damage.

We found that the female gender, the follow-up time, and musculoskeletal attack dominance were independent predictors of both the ADDI and modified ADDI. The greater frequency of reproductive problems in women, which we examined in a previous study with the same cohort (11), might explain why the female gender was an independent predictor of damage. Diagnostic delay and colchicine non-adherence were only associated with the ADDI, while a family history of amyloidosis was associated with the modified ADDI.

There were additional valuable findings in our study. First, patients who had a classical FMF phenotype of serositis were less likely to develop damage. Supporting this observation, peritonitis was significantly more frequent in patients without damage. Compared to other disease manifestations, management of patients with peritonitis may be done better by both patients and physicians. A previous study re-

ported that patients with amyloidosis had less peritonitis and more arthritis compared to those without amyloidosis (41), which supports our findings. Second, having over 11 years of education was inversely associated with damage according to the ADDI and modified ADDI, which supports the idea that high sociocultural status reduces the risk of future damage.

The major limitation of our study is its cross-sectional design. An inception cohort study design would provide further and more definitive information. Another limitation of our analysis is that serum amyloid A (SAA) levels were not measured to determine persistent inflammation; however, high concordance between CRP and SAA has been reported recently (42, 43).

Our study is the first to analyse cumulative damage in FMF patients and to apply comprehensive damage indexes, such as the ADDI and modified ADDI, to FMF patients, particularly those with colchicine resistance and/or those who were treated with targeted biologic treatments. This study might act as a reference point for comparing other real-life cohorts and the temporal effects of treatments. We defined independent risk factors for damage accrual in patients with FMF, which will help to ensure better qualified management of FMF. The association between severe disease features and damage defined only by the modified ADDI justifies concerns about musculoskeletal pain as a damage item and might point to the need for a re-evaluation of the ADDI for FMF patients.

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