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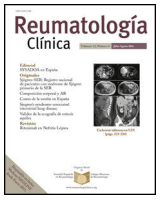

Brief report

Familial mediterranean fever patients may have unmet needs for the treatments of exertional leg pain and enthesitis

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ABSTRACT

Introduction: Exertional leg pain (ELP) and enthesitis are musculoskeletal findings in familial Mediterranean fever (FMF). They are not accepted as principal treatment targets. In this study, we assessed the effectiveness of treatments on ELP and enthesitis.
Material and methods: We have included 218 FMF patients to the study. We retrospectively compared the FMF attacks' frequency, duration and intensity (FMF attack VAS score) and levels of ELP VAS and enthesitis VAS scores between pre-treatment stage and while patients were on treatment at the last visit.
Results: Forty-nine (22.5%) and 52 (23.9%) of the patients had enthesitis and ELP respectively. All patients were on colchicine treatment. Serositis attacks respond the treatments significantly. Moreover, both ELP VAS scores ($p = 0.002$) and enthesis VAS scores ($p = 0.17$) were improved with treatment. But only improvement in ELP VAS scores was significant.
Conclusion: FMF treatments had favourable effect on ELP and enthesitis in FMF patients. However, the response rates would be inadequate. Therefore, there would be unmet need for treatment of both conditions.

Los pacientes con fiebre mediterránea familiar podrían tener necesidades no satisfechas de tratamiento del dolor en piernas con el esfuerzo y entesitis

Palabras clave:
Fiebre mediterránea familiar
Entesitis
Dolor en piernas con el esfuerzo
Escala analógica visual

RESUMEN

Introducción: El dolor en piernas con el esfuerzo (ELP) y la entesitis son hallazgos musculoesqueléticos en la fiebre mediterránea familiar (FMF), no aceptados como dianas de tratamiento principales. En este estudio evaluamos la efectividad de los tratamientos para ELP y entesitis.
Material y métodos: Incluimos en el estudio a 218 pacientes con FMF. Comparamos retrospectivamente la frecuencia de los ataques de FMF, su duración e intensidad (escala analógica visual [VAS] del ataque de FMF) y los niveles VAS para ELP y las puntuaciones VAS para entesitis entre la etapa previa al tratamiento y la etapa en que los pacientes estaban siendo tratados en la última visita.
Resultados: Cuarenta y nueve (22,5%) y 52 (23,9%) pacientes tuvieron entesitis y ELP, respectivamente. Todos los pacientes recibieron colchicina. Los ataques de serositis respondieron significativamente a los tratamientos. Además, tanto las puntuaciones VAS para ELP ($p = 0{,}002$) como para entesis ($p = 0{,}17$) mejoraron con el tratamiento, pero únicamente fueron significativas las puntuaciones VAS para ELP.
Conclusión: Los tratamientos para FMF tuvieron un efecto favorable para ELP y entesitis en los pacientes con FMF. Sin embargo, las tasas de respuesta serían inadecuadas. Por tanto, existiría una necesidad no satisfecha de tratamiento de ambas situaciones.

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Introduction

Familial Mediterranean fever (FMF) is an auto-inflammatory disease which has the features of recurrent attacks with fever, serositis, musculoskeletal findings and erysipelas like erythema.[1] Non-recurrent musculoskeletal findings including arthralgia, enthesitis, exertional leg pain (ELP), myalgia, sacroiliitis and lower extremity sinovitis would be also frequently detected in FMF.[2] Colchicine is the gold standard treatment for FMF. However, 5% of the FMF patients do not respond to the colchicines treatment while taking highest tolerable dosage.[3,4] Furthermore, definition of colchicine resistance has been mainly defined based upon the classical attacks' frequency and/or intensity.[3] However, both enthesitis and ELP would not be a part of classical attacks which were characterised by serositis. Herein, those finding usually manifest as chronic and continuous manner.[5,6] Therefore, enthesitis and ELP would be overlooked while considering treatment response to colchicine in FMF patients. Also, in FMF patients both conditions would be accepted as musculoskeletal manifestations of distinctive spondiloarthropathy (SpA) form. Hereby, ELP would be accepted as a sign of lower extremity enthesitis.[6] Therefore, both conditions would be assessed together with serositis attacks while evaluating the FMF treatments' effectiveness.

Even though, colchicine is the mainstay remedy for FMF related serositis, as far as we know, there is no study in the literature that evaluated the effect of colchicine or other FMF treatment options on enthesitis and ELP in FMF patients.

In this study, we evaluated the validity of the hypothesis: "FMF treatments would be effective in both enthesitis and ELP in FMF patients."

Material and methods

We have enrolled 218 FMF patients who fulfilled the Modified Tel-Hashomer criteria.[7] All consecutive FMF patients who attended to the rheumatology outpatient clinic in the last six months and gave consent were included in the study. Patients were excluded if their ages were out of the range 18–65 years, nursing and pregnant. Furthermore, patients with concomitant spondiloarthropathy and another inflammatory musculoskeletal disease in their medical history were also excluded. The patients eligible to the study were firstly evaluated by physical examination for ruling out vascular, neurologic and other musculoskeletal conditions related to ELP and enthesitis. The patients with any of those conditions that would account for ELP or enthesitis were excluded. All patients have been taking appropriate and maximal tolerated colchicine dosage required for maintaining permanent remission at stable dosing for at least six months. According to treatment protocol of our clinical centre, maximal applied colchicine dosage is 3 mg/day. Furthermore, interleukin-1 blocker treatments were implemented to the patients who had resistance or intolerance to maximal dosage of colchicine treatment.

In this study, we have evaluated the patient's global assessment of FMF attack, ELP and enthesitis with visual analogue score (VAS). We used Bath Ankylosing Spondylitis Disease Activity Index's fourth question to evaluate enthesitis VAS in FMF patients.[8] Patients indicated the scores by making a handwritten mark on a 10-cm line that represents a continuum between 0 and 100. Herein, zero being no problem and 100 being the worst problem.

We have evaluated all FMF patient's demographic parameters, FMF related features (disease duration, attacks' features, other FMF-related symptoms, attacks' frequency per year, VAS attack scores, amyloidosis, daily colchicine dosage, MEFV mutations if available, Il-1 blocker treatment) and co-morbidities (hypertension, hypothyroidism, hyperthyroidism, cardiovascular diseases, coronary artery diseases, cerebrovascular diseases, chronic renal disease, chronic obstructive pulmonary disease, diabetes mellitus). The international severity scoring system (ISSF) was used for assessing the severity of the disease.[9] Moreover, we examined ELP VAS scores in only patients with ELP and enthesitis VAS scores in only patients with enthesitis. Furthermore, for evaluating treatments' effect on those disease features, we questioned the patients for VAS scores and attack's properties before and at the last visit under treatment.

ELP was defined as pain distal to knee and proximal to ankle joint that is related to exertion.[10] Furthermore, complaints of pain, tenderness, stiffness or swelling around heel, knee, hip, toe, elbow, backbone, and the sole of the foot would be accepted as enthesitis. Both conditions were diagnosed in the patients based upon history.

In this study, we assessed the response of the patients' serositis attacks, ELP and enthesitis to the FMF treatments with comparing pre and post treatment ELP and enthesitis VAS scores and serositis attacks features.

This study was approved by the Local Research Ethics Committee and carried out in compliance with the Helsinki Declaration. All the patients gave written informed consent.

Statistical analyses

Statistical analyses were carried out using SPSS Version 17.0 (SPSS Inc., Chicago, IL, USA). In order to determine if the data were normally distributed, the Kolmogorov–Smirnov test was performed. All of the parameters did not distribute normally. Therefore, comparisons of the dependent continuous variables (VAS scores, attacks' frequency and duration before and during treatment) were performed by Wilcoxon test. The results are given as mean ± standard deviation. *p*-Value lower than 0.05 was considered as statistically significant.

Results

In our FMF cohort, 139 (63.7%) of 218 patients were female. Most frequent FMF related symptoms were peritonitis (86.7%), fever (61.5%) and pleuritis (33.9%). Herein, forty-nine (22.5%) of 218 patients had complaints compatible with enthesitis. Furthermore,

Table 1
Demographic and disease related features of the FMF patients.

	n = 218
Demographic features	
Age (years)	36.1 ± 11.3
Gender (M/F)	79/139
Disease duration (years)	9.1 ± 7.2
Co-morbidities (%)[a]	46(21.1)
Disease related features	
Peritonitis (%)	189(86.7)
Pleuritis (%)	74(33.9)
Fever (%)	134(61.5)
Arthritis (%)	63(28.9)
Erysipeloid erythema (%)	48(22.0)
Exertional leg pain (%)	52(23.9)
Myalgia (%)	56(25.7)
Enthesitis (%)	49(22.5)
Amyloidosis (%)	8(3.7)
MEFV exon 10 homozygote (%)	52(23.9)
ISSF score (0–10)	1.2 ± 1.2
Colchicine dosage (mg/day)	1.3 ± 0.4
Il-1 blockers	3(1.3)

M: male; F: female; FMF: familial Mediterranean fever; ISSF: the international severity scoring system.

[a] Hypertension, hypothyroidism, hyperthyroidism, cardiovascular diseases, coronary artery diseases, cerebrovascular diseases, chronic renal disease, chronic obstructive pulmonary disease, diabetes mellitus.

Table 2
Treatments effect on the FMF attacks' features.

	Pre-treatment	Treatment	*p*
Attack frequency (per year)	19.4 ± 16.6	2.8 ± 4.5	**<0.001**
Attack duration (day)	3.6 ± 2.2	1.3 ± 1.6	**<0.001**
VAS attack score (0–100)	90.2 ± 14.3	29.0 ± 32.5	**<0.001**
VAS enthesitis score (0–100)*	51.5 ± 34.9	43.1 ± 27.5	0.17
VAS exertional leg pain (0–100)**	53.0 ± 40.7	39.4 ± 34.5	**0.002**

VAS: Visual analogue score.
* VAS enthesitis scores were evaluated in 49/218 of the FMF patients.
** VAS exertional leg pain scores were evaluated in 52/218 patients.
At the time of last visit
$p < 0.05$ was shown bold letters.

52 (23.9%) of the patients have been suffering from ELP. The patients' demographic features and disease related properties were shown in Table 1.

All patients were on colchicine during the study. Mean colchicines dosage was 1.3 ± 0.4 mg/day. Furthermore, three patients have been using any of Il-1 blockers concomitant with colchicine at the time of the study. Herein, we showed that frequency, duration and intensity of the FMF attacks were significantly decreased with FMF treatment. Also, treatments had significant favourable effect on the patients' ELP VAS scores. However, enthesitis VAS scores decreased non-significantly in the course of the treatment (Table 2). Notwithstanding, none of the FMF patients either with ELP or enthesitis were completely recover from those findings with FMF treatment. Moreover, the three patients on Il-1 blockers had similar response to treatment as compared to rest of the patients in terms of ELP and enthesitis VAS scores.

Discussion

In this study, we found that in the study cohort, FMF treatment had significant favourable effect on ELP. However, the improvements in enthesitis scores were not statistically meaningful.

Improvements in both ELP and enthesitis VAS scores were not more than 25% in absolute numbers. Nevertheless, FMF treatment decreased VAS attack scores to one-thirds of the pre-treatment levels. Therefore, it would be speculated that there would be unmet need for ELP and enthesitis treatment in FMF patients.

Both ELP and enthesitis were not uncommon musculoskeletal findings in FMF patients. Several former studies have shown that enthesitis would be detected as far as two thirds of the FMF patients.[11] Moreover, up to half of the FMF patients would suffer from ELP.[5,6] In our study, more than one fifth of our patients had either ELP or enthesitis. In former studies, it was shown that colchicine has not remitted musculoskeletal symptoms in the SpA patients with FMF.[12] Furthermore, there were no studies in the literature primarily focused on effect of treatment on enthesitis and ELP in FMF patients. Herein, our findings were similar with studies on patient with both SpA and FMF. Even if, FMF treatments would have somewhat favourable effects on ELP and enthesitis, the patients continue to suffer from those conditions unlike serositis attacks.

The main goals of the treatment in FMF were preventing serositis attacks and amyloidosis.[13] Therefore, chronic musculoskeletal findings of the disease would be underestimated. The clinicians would be reluctant to change their treatment approach according to chronic findings. Likewise, in our study, the mean colchicine dosage in the patients with ELP or enthesitis was 1.4 ± 0.3 mg/day and not statistically different from the rest of the group. Therefore, increasing colchicine to the highest tolerable dosages or implementing disease modifying drugs or anti-tumour necrosis therapies would be treatment options for ELP and enthesitis.

There study had some limitations. Firstly, the study was conducted retrospectively. Therefore, pre-treatment data depended on the patients' statement. Furthermore, enthesitis and ELP in the patients were diagnosed as history, instead of examination. However, our data would have shown the patient's perception about the treatments' effect on ELP and enthesitis. Furthermore, according to our treatment protocol, we mainly adjusted the colchicines dosage according to serositis attacks. Therefore, increasing the colchicines dosage of the patients to highest tolerable dosages up to 3 mg/day would improve the response of the therapies to ELP and enthesitis. Finally, we did not evaluate the effect of other drugs, including non-steroidal anti-inflammatory drugs on enthesitis severity.

Consequently, even though FMF treatments had a positive impact on ELP and enthesitis in FMF patients, the responses would be accepted inadequate as compared to response for serositis. Therefore, there would be unmet need for treatment of ELP and enthesitis in FMF patients and new treatment approaches should be implemented for those findings.

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Authors' contributions

MET: Main writer, planning methodology to reach the conclusions and reviewing the article before submission scientifically besides spelling and grammar; OV: Planning methodology to reach the conclusions; RM: Taking responsibility in logical interpretation and conclusion of the results; NS: provide important contributions to conceptual or planning stages of the study or collection/processing, analysis or interpretation of the data; SYO: Reviewing the article before submission scientifically besides spelling and grammar.

Conflicts of interest

Authors have nothing to disclose.

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