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Original article

Evaluation of frequency and the attacks features of patients with colchicine resistance in FMF

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ABSTRACT

Introduction: Colchicine is the mainstay for the treatment of FMF, which is an auto-inflammatory disease mainly with relapsing polyserositis. Despite daily doses of 2 mg or more each day, approximately 5% to 10% of the patients continue to suffer from its attacks. In this study, we aimed to investigate the depression and attack features in patients with FMF who have colchicine resistance (CR).

Patients e Methods: CR was defined for FMF patients with 2 or more attacks within the last 6 months period while using 2 mg/day colchicine. Eighteen patients (9 Female/9 Male) were enrolled into the CR group and 41 patients were enrolled into the control group (12 Male/29 Female). Demographic, clinical e laboratory findings, treatment adherence, and *the Beck Depression Inventory (BDI)* scores were evaluated.

Results: The age of onset of FMF was significantly lower in the CR group (12.3 yrs vs. 16.9 yrs, $P = 0.03$). Disease duration was longer in the CR group ($P = 0.01$). Abdominal and leg pain due to exercise were significantly more frequent in the CR group versus controls (83% vs. 51%; $P = 0.02$ e 88% vs. 60%; $P = 0.04$, respectively). Patients with BDI scores over 17 points were more frequent in the CR group compared to controls (50% vs. 34.1%; $P < 0.001$).

Discussion: We found that: (1) the age of disease onset was lower and (2) the disease duration was longer in CR group. Pleuritic attacks, hematuria e proteinuria were more frequent in CR patients. We propose that depression is an important factor to consider in the susceptibility to CR.

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Avaliação da frequência e aspectos dos ataques de pacientes com resistência à colchicina em febre familiar do Mediterrâneo (FFM)

Palavras-chave:
Febre familiar do Mediterrâneo
Resistência à Colchicina
Tratamento
Depressão

RESUMO

Introdução: Colchicina é a viga-mestra para o tratamento de FFM, que é uma doença autoinflamatória com polisserosite recidivante como principal manifestação. Apesar de doses diárias de 2 mg ou mais/dia, aproximadamente 5%-10% dos pacientes continuam a sofrer de seus ataques. Neste estudo, objetivamos investigar os aspectos da depressão e dos ataques em pacientes com FFM apresentando resistência à colchicina (RC).

Pacientes e Métodos: Em pacientes com FFM, RC foi definida como dois ou mais ataques nos últimos seis meses, quando em medicação com colchicina 2 mg/dia. Dezoito pacientes (nove mulheres e nove homens) foram recrutados no grupo RC e 41 pacientes no grupo de controle (29 mulheres/12 homens). Foram avaliados os achados demográficos, clínicos e laboratoriais, a fidelidade ao tratamento e os escores do *Beck Depression Inventory* (BDI).

Resultados: A idade de surgimento da FFM foi significativamente menor no grupo RC (12,3 anos *vs.* 16,9 anos, P = 0,03). A duração da doença foi maior no grupo RC (p = 0,01). Dores abdominais e nas pernas em decorrência do exercício foram significativamente mais frequentes no grupo RC *versus* controles (83% *vs.* 51%; p = 0,02 e 88% *vs.* 60%; p = 0,04, respectivamente). Pacientes com escores BDI > 17 pontos foram mais frequentes no grupo RC *versus* controles (50% *vs.* 34,1%; p < 0,001).

Discussão: Verificamos que: (1) a idade do surgimento da doença foi mais baixa e (2) a duração da doença foi maior no grupo RC. Ataques pleuríticos, hematúria e proteinúria foram mais frequentes em pacientes com RC. Propomos que a depressão é fator importante a ser levado em consideração na sensibilidade à RC.

Introduction

Familial Mediterranean fever (FMF) is a hereditary and an auto-inflammatory disease predominantly characterized by repeated attacks of fever, abdominal pain, pleuritic chest pain, arthritis, and erysipelas-like erythema. The disease is most prevalent among non-Ashkenazi Jews, Arabs, Turks, and Armenians.[1] The pathogenesis is mainly based on the absence or insufficiency of pyrin production, which is a peptide involved in the inflammatory cascade that inhibits complement 5a (C5a). The main mechanisms that trigger FMF attacks have not been established. Colchicine is still the mainstay in the treatment of the disease. It completely or partially prevents FMF attacks and subsequent reactive amyloidosis that is regarded as the most dangerous complication of FMF.[2]

Interestingly, colchicine resistance (CR) is prevalent in nearly 10% of the FMF patients. The attack frequency or intensity may go on with similar or diminished frequency and severity. The CR patients could be divided into complete or partially non-responders. Many factors might be involved in the CR, including genetic predisposition as well as environmental and psychiatric conditions. Still, little is known about the absolute etiology of CR in FMF patients. Treatment adherence and potential reasons including demographical factors, socio-economic status, clinical and laboratory factors, and psychiatric dynamics are thought to be contributing factors.

The Beck Depression Inventory (BDI) was developed by Beck and colleagues (1979) and adapted to Turkish by Hisli (1988). The BDI is a self-report scale of 21 items measuring the emotional, somatic, cognitive, and motivational symptoms exhibited in depression. The scale is not designed to diagnose depression but to objectively determine the severity of depressive symptoms. Correlation coefficients between the English and Turkish versions of the scale were calculated as 0.81 and 0.73 (language validity); split half reliability was 0.74, and criterion-related validity with MMPI-D (Minnesota Multiphasic Personality Inventory) was 0.63. The BDI scores ≥ 17 were reported to discriminate depression that might require treatment with more than 90% accuracy. The score of each item ranges from 0 to 3, and the depression score is obtained by adding the score of each item. The highest obtainable score is 63.[3,4]

As a consequence, different therapeutic strategies are ongoing to limit CR in FMF patients. In this study, we aimed to investigate the depression and attack features in patients with FMF who have the CR.

Patients and methods

The study group was composed of 59 FMF patients with 18 CR (9 female / 9 male) and 41 (12 male / 29 female) complete colchicine responders. Patients having other accompanying diseases including infections, malignancies, autoimmune or metabolic diseases and patients who were diagnosed for depression previously and under-treatment with antidepressants were excluded. The diagnosis was checked one more time through the re-questioning of the patients in accordance with the Livneh criteria of FMF.[5]

CR was defined as two or more FMF attacks in a six-month period following a twelve-month regular therapy. Patients

Table 1 – Demographic features of CR group and control group.

	CR Group (n = 18)	Control Group (n = 41)	p values
Current age (age ± SD)	30.1 ± 10,5	28.2 ± 9.3	0.5
Gender (F/M)	9/9	29/12	0.12
Monthly income over 1000 TL	5 (27.7%)	10 (24.3%)	0.78
# of married subjects	5 (27.7%)	22 (53.6%)	0.59
Educational status (undergraduates)	5(27.7%)	9 (21.9%)	0.62
# of unemployed subjects	2 (11.1%)	8 (19.5%)	
# of kids (number ± SD)	1 ± 1.5	0.9 ± 1.3	0.8
Subjects with family history of FMF	13 (72.2%)	27 (65.8%)	0.6
Age of FMF Diagnosis	20.6 ± 8.6	21.9 ± 10	0.6
Time between onset and diagnosis (months)	92	59.3	0.2
Diseases duration (months)	212	133	0.01

CR, Colchicum resistant; TL, Turkish Lira.

with ≤ 1 FMF attack within the six months or without any attacks over the twelve months were randomized into the control group. Patients in the colchicine resistance group were using 2 mg/day and higher doses, and in the control group patients were using colchicine below the doses of 2 mg/day. The demographic data, adherence to treatment, clinical and attack features of the disease including the leg pain and amyloidosis, laboratory findings, and BDI scores, alcohol, and narcotic usage were recorded. A BDI score > 17 was considered significant for severe depression that requires treatment.

The age of disease onset as well as diagnosis and the time period from symptoms to diagnosis were carefully questioned. The demographic data included socio-economic features such as monthly income, education and literacy, marital status, number of children, and employment. Patients were compared by the minimum wage in our country for their economic status. Concerning the educational status, post-graduate patients were compared with each other. Urine analyses were assessed with a dipstick during attacks and were collected from files.

The local ethical committee approved the study protocol and all the participant consent forms were collected. Student's *t* test and one-way ANOVA were used for comparison of averages. Pearson's correlation analyses were performed to evaluate other factors. P value of < 0.05 was accepted as statistically significant.

Results

While CR patients were regularly implementing the treatment protocol during the 6-month follow-up, 40% of the patients in control group were misusing the drugs. Baseline demographic features of both groups are demonstrated in Table 1. There was no statistically significant difference between the groups concerning the monthly income, educational and marital status, number of kids, and employment. Distribution of the patients with family history of FMF was similar. Disease onset age was significantly lower in CR group in contrast to the controls (12.3 years and 16.9 years; $p = 0.03$) and disease duration was significantly longer in CR group (212 months and 133 months; $p = 0.01$). There were similar results concerning the time from disease onset to diagnosis, and the difference was not significant between the groups. When we compared the accompanying complaints during the attacks, pleuritic chest pain, erysipelas-like erythema and effort associated, leg pain was significantly more frequent in CR group (83% and 51% $p = 0.02$; 16.6% and 2.4% $p = 0.04$; 88% and 60% $p = 0.04$; respectively). Moreover, transient proteinuria and hematuria were significantly more frequent in CR group ($p = 0.006$). There was not a valuable difference between the groups concerning abdominal pain and arthritis (Table 2). There were no alcohol or narcotics history among the groups. The number of patients with amyloidosis in both groups was similar (Table 2). There was no renal insufficiency in both groups. Patients with BDI scores over 17 points were more frequent in the CR group compared to the controls (50% *vs* 34.1%; $p < 0.001$).

Discussion

This prospectively designed study attempts to evaluate the factors that may lead to CR among the FMF patients. Disease onset age was significantly lower in CR group in contrast to the control, and disease duration was significantly longer in CR group. Questionnaire results showed that patients in CR group were receiving their drugs regularly under full drug compliance. Patients with infrequent attacks forgot to take the colchicine. Additionally, there were no alcohol or narcotics history among the CR patients. In fact, the main triggering etiological factors behind CR are not known. In the previous study, Lidar *et al.* found that patients with severe FMF prognosis had more CR.[6] These findings are in good agreement with our study. Obviously, patients with long disease duration, high BDI scores, were significantly more frequent in the CR group. And attacks in CR group were more severe than control group. When we compared the accompanying complaints during the attacks, pleuritic chest pain, erysipelas-like erythema, and effort associated leg pain were more frequent in CR group. Moreover, proteinuria and hematuria presence during the attacks were more frequent in CR group. Also Lidar *et al.* demonstrated that the abdominal attack, chest pain, and arthritis were more frequent and severe in CR group, while erysipelas-like erythema attacks were similar in both groups. The presence of depression could increase the frequency of FMF attacks or the combination of frequent FMF attacks and inflammatory pain might cause depression. The activity of serotonergic inflammatory cascade has been speculated to

Table 2 – Symptomatic features of all patients.

	CR Group (n = 18)	Control Group (n = 41)	p values
Abdominal attack	16 (88.8%)	39 (95.1%)	0.38
Joint attack	14 (77.7%)	30 (73.1%)	0.7
Chest attack	15 (83.3%)	21 (51.2%)	0.02
Erysipela-like erythema	3 (16.6%)	1 (2.4%)	0.04
Effort associated leg pain	15 (83.3%)	25 (60.9%)	0.04
Presence of transient hematuria and proteinuria during the attacks	8 (44.4%)	5 (12.1%)	0.006
of patients with amyloidosis	3 (16.6%)	2 (4.8%)	0.13
of family members with amyloidosis	2 (11.1%)	1 (2.4%)	0.16

provoke the FMF attacks.[7] It was demonstrated that initiating selective serotonin reuptake inhibitors (SSRI) decreases the frequency of FMF attacks with CR.[8] Accordingly, it was shown that stress factors facilitate depression and increase the secretion of inflammatory cytokines.[9] There are studies arguing the role of depression in the severity of FMF and that depression treatment also diminishes the number of attacks. These findings reveal the role of depression in CR.[8]

Increases in inflammation can affect the pathophysiology of the depression.[8] In cytokine based FMF studies, plasma concentrations of interleukin-2 (IL), IL-12, IL-18 and tumor necrosis alpha (TNF-α) were elevated in depressive patients.[10,11] The pro-inflammatory cytokine, IL-12, was elevated both during the attacks and in the attack free period, contrasting healthy control studies.[12] In addition to IL-12 secretion, cytotoxic T cells IL-2, IFN gamma, and TNF-alpha also increased in FMF patients. These cytokines were elevated both in FMF and depression. Our study has a limitation for the MEFV mutations of the patients that didn't hold for all of the patients enrolled into the study. But our aim was the investigation of other factors affecting CR.

Consequently, we can argue that depression is an important reason among the factors that may lead to CR. Consistent with previous studies, we have found out the CR patients' depression findings are more severe than the controls. Clinicians should consider the initiation of SSRI in colchicum resistant patients. We found that disease onset age was lower and disease duration was longer. In addition, pleuritis attacks, transient microscopic hematuria, and proteinuria were more frequent in CR patients during attack episodes. Further large-scale screening is required.

Conflicts of interest

The authors declare no conflicts of interest.

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