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Original article

Is there a relationship between gouty arthritis and Mediterranean fever gene mutations?

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ABSTRACT

Objective: Gouty arthritis and familial Mediterranean fever share some clinical and pathological features such as being classified as auto-inflammatory disease, association with inflammasome, short-lived intermittent arthritis, and good response to colchicine and anti-interleukin-1 treatments. As Mediterranean fever gene is the causative factor of familial Mediterranean fever, we aimed to investigate the prevalence of Mediterranean fever gene mutations and their effect on disease manifestations in Turkish gouty arthritis patients.

Methods: Ninety-seven patients diagnosed with primary gouty arthritis (93 M and 4 F, 54 [37–84] years) and 100 healthy controls (94 M and 6 F, 57 [37–86] years) were included in the study. All subjects were genotyped for the Mediterranean fever gene variations. Number of gout attacks, diuretic use, history of nephrolithiasis and presence of tophus were also recorded.

Results: The carriage rate of Mediterranean fever mutations for patients and controls was 22.7% ($n = 22$) and 24% ($n = 24$), respectively. The comparison of the patient and control groups yielded no significant difference in terms of the Mediterranean fever mutations' carriage rate ($p = 0.87$). The allelic frequencies of the Mediterranean fever mutations in patients were 11.9% ($n = 23$) and 14% ($n = 28$) in controls ($p = 0.55$). The presence of Mediterranean fever variants did not show any association with clinical features of gouty arthritis. The subgroup analysis of patients revealed that gouty arthritis patients with mutations had similar frequencies of tophus, history of nephrolithiasis and podagra compared to the ones without mutations ($p > 0.05$).

Conclusions: This study does not provide support for a major role of Mediterranean fever mutations in Turkish gouty arthritis patients.

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Existe uma relação entre a artrite gotosa e as mutações genéticas da febre familiar do Mediterrâneo?

Palavras-chave:
Artrite gotosa
Proteína *MEFV*
Febre familiar do Mediterrâneo

RESUMO

Objetivo: A artrite gostosa e a febre familiar do Mediterrâneo (FFM) compartilham algumas características clínicas e patológicas, como ser classificada como uma doença autoimune inflamatória, ter associação com o inflamassoma, manifestar artrite intermitente de curta duração e boa resposta a tratamentos com colchicina e anti-interleucina-1. Como o gene da febre familiar do Mediterrâneo (*MEFV*) é o fator causador da FFM, este estudo teve como objetivo investigar a prevalência de mutações do gene *MEFV* e seu efeito sobre as manifestações da doença em pacientes turcos com artrite gotosa.

Métodos: Foram incluídos no estudo 97 pacientes com diagnóstico de artrite gotosa primária (93 M e 4 F; 54 [37-84] anos) e 100 controles saudáveis (94 M e 6 F; 57 [37-86] anos). Todos os indivíduos foram submetidos à análise do genótipo à procura de variações no *MEFV*. Também foi registrado o número de crises de gota, o uso de diuréticos e a história de nefrolitíase e presença de tofos.

Resultados: A frequência de portadores de mutações no *MEFV* em pacientes e controles foi de 22,7% (n = 22) e 24% (n = 24), respectivamente. A comparação entre os pacientes e os controles não produziu diferença estatisticamente significativa em termos de frequência de portadores de mutações no *MEFV* (p = 0,87). As frequências alélicas de mutações no *MEFV* nos pacientes foram de 11,9% (n = 23) e 14% (n = 28) nos controles (p = 0,55). A presença de variantes do *MEFV* não mostrou qualquer associação com as características clínicas da artrite gotosa. A análise por subgrupos de pacientes revelou que aqueles com artrite gotosa com mutações tinham frequências semelhantes de tofo, história de nefrolitíase e podogra em comparação com os indivíduos sem mutações (p > 0,05).

Conclusões: As mutações no gene *MEFV* não exercem um papel relevante em pacientes turcos com artrite gotosa.

Introduction

Gouty arthritis is one of the most frequently observed inflammatory arthritis in the world. Although its epidemiology shows significant ethnical variations, it is affecting at least 1–2% of men in the western world.[1] Gouty arthritis has some classical clinical findings such as acute painful attacks of arthritis in the joints (especially the first metatarsal joint of the foot), mono-articular involvement and intermittent pattern.[2] It is caused by the deposition of monosodium urate monohydrate (MSU) crystals in the joints. MSU crystals induce a variety of inflammatory cytokines particularly interleukin-1 (IL-1).[3] In addition, recent reports revealed a major role for inflammasome activity in the development of gout attacks.[3] On the other hand, familial Mediterranean fever (FMF) is the most commonly seen periodic fever syndrome.[4] FMF is caused by the mutations (single substitutions) in the *MEditerranean FeVer (MEFV)* gene at the short arm of the 16th chromosome.[4] This gene encodes a protein called pyrin. Under normal circumstances, pyrin limits the activation of the NLRP3-inflammasome. It is presumed that the mutated pyrin protein in FMF is theoretically not able to suppress the inflammasome, and thus the inflammatory response develops.[5] Both gouty arthritis and FMF share some clinical and pathogenic mechanisms such as short-lived and intermittent arthritis, association with inflammasome and response to colchicine and anti-IL-1 therapies.[3,6] To the best of our knowledge, there has been no previous study about the association between *MEFV* gene mutations and gouty arthritis. In this study, we aimed to investigate the prevalence of *MEFV* gene mutations and their effect on disease manifestations in Turkish gouty arthritis patients.

Methods

Sample size calculation

The sample size was calculated by using the results of previous studies that investigated the frequency of *MEFV* mutations in patients with inflammatory rheumatic diseases and healthy controls.[7,8] According to the analysis, based on $\alpha = 0.05$ and a power of 80%, at least 89 subjects were needed per group.

Patients and controls

Ninety-seven unrelated patients diagnosed with primary gouty arthritis were recruited from the outpatient clinic of Gulhane Military School of Medicine Department of Rheumatology (Ankara, Turkey). The clinical diagnosis of gout was established by the revised American College of Rheumatology classification criteria.[9] Patients were also questioned for the presence of the Tel-Hashomer criteria for diagnosis of FMF.[10] Sex, age, number of gout attacks, diuretic use, and history of nephrolithiasis and presence of tophus were also collected.