Patients with FMF Associated Spondyloarthropathy Who Has Heterozygous M694V Mutation: A Case Report

Heterozygous M694V Mutasyonu Olan FMF İlişkili Spondiloartropatili Hastalar: Bir Olgu Sunumu

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Keywords

Familial Mediterranean Fever (FMF), spondyloarthropathy (SpA), M694V mutation, sacroiliitis

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Abstract

Familial Mediterranean Fever (FMF) is the most common Periodic Fever syndrome characterized by attacks like serositis and fever. FMF is an autosomal recessive disease caused by *MEFV* gene mutations which located on 16p13.3. Spondyloarthropathy (SpA) is a chronic rheumatic disease characterized by inflammation in axial and peripheral joints with enthesitis and extraarticular involvements. One of the major criteria of SpA is sacroiliitis that can be described rarely in FMF patients. *M694V* mutation has been frequently seen mutation in FMF patients; also it has been associated with SpA. In this article, we present a case of a patient with heterozygous *M694V* mutation FMF and SpA combination.

Öz

Ailesel Akdeniz Ateşi (FMF) serozit ve ateş atakları ile karakterize en sık görülen Periyodik Ateş sendromudur. FMF 16p13.3 üzerinde lokalize olan *MEFV* gen mutasyonundan kaynaklanan otozomal resesif geçen bir hastalıktır. Spondiloartropati (SpA) aksiyel eklemlerde enflamasyon, periferik oligoartrit, entezit ve ekstraartiküler bulgularla seyreden kronik romatolojik bir hastalıktır. SpA'nın tanı koydurucu özelliği olan sakroiliit, ve FMF hastalarında da nadir de olsa görülmektedir. FMF hastalarında sık görülen bir mutasyon olan *M694V* mutasyonu ile spondiloartrit birlikteliği görülmektedir. Bu çalışmada, heterozigot *M694V* mutasyonu olan hastada FMF ile SpA birlikteliğini sunduk.

Introduction

Familial Mediterranean Fever (FMF) is an autoinflammatory inherited disorder characterized by recurrent attacks of abdominal and chest pain, joint swelling and pain, erysipela-like skin disease associated

with fever. The typical symptoms approximately last one to three days and resolves spontaneously (1).

The disease has been primarily identified in several ethnic groups like Sephardic Jews, Armenians, Turks and Arabs communities and autosomal, recessively inherited autoinflammatory disease caused by *MEFV* gene missense variations which is located on the short arm of chromosome 16. *M694V* is the most common mutation in the *MEFV* gene (2,3).

Spondyloarthropathy (SpA) is a chronic rheumatic disease that characterized by musculoskeletal involvement and also extra-articular involvements that closely related with Human Leukocyte Antigen (HLA)-B 27 (4).

Inflammatory back pain with spinal involvement, sacroiliitis and enthesitis have been rarely seen in FMF (5). Recent data has indicated potential association between SpA and FMF. HLA-B27 negativity may be seen as the main feature of FMF related SpA. It has been shown in the literature *M694V* mutation might be associated with the development of enthesopathy (6).

We report a case with heterozygous mutation of *M694V* in FMF related with SpA.

Case Report

Fifty-three-year-old male was admitted to the clinic with a history of low back pain which worsened with inactivity and improved with exercise. Morning stiffness has been often longer than 45 minute for nearly ten years and bilateral heel pain for one-years. The complaint of back pain and morning stiffness has increased recently. He has not described any episodes of acute abdominal pain and fever for two years.

In his past medical history, at age 25, although he underwent an appendectomy because of persistent abdominal pain, his intermittent attacks of acute abdominal pain and fever still in progressed. After that operation because of the persistent complaints he had been diagnosed as FMF and had been begun colchicine 1.5 mg/day and a non-steroidal anti-inflammatory drug. But he has been used these drugs irregularly since then.

His family history was evaluated and his wife had a disease carrier with *M694V* heterozygous mutation, but she had no symptoms so far and there was no relationship between them. He had five children and all of them had some similar complaints like their

father, however their typical serositis complainments were more dominant, they had no low back pain and X-ray findings were not meaningful for sacroiliitis. Their inflammatory markers were negative.

At his physical examination, his general appearance was good. Vital examination was normal. His lumbar movements have been restricted (Schober test 2.5 cm) and chest expansion was normal according to the age. Tragus to wall and occiput to wall distance increased slightly. Straight leg raising test and femoral stretch test was negative. Sacral compression test was bilaterally positive. He had tender on the enthesopathic areas of the bilateral plantar fascia with palpation. Other pathological findings weren't detected during his systemic examinations.

Laboratory investigations revealed a normal complete blood cell count, and electrolyte values. He was using non-steroid drugs for pain medication, we identified normal sedimentation and C-reactive protein values with non-steroid drugs used. Agglutination test for Brucellosis were negative. Twenty-four hours of total protein in the urine increased slightly, 109 mg/24 h (normal value: 50-100 mg/24 h). The genetic analysis revealed heterozygous *M694V* mutation, despite HLA-B27 was negative.

A radiological examination of sacroiliac joint was showed bilateral sacroiliac joint narrowing, with erosions and sclerosis (Figure 1). T2-weighted magnetic resonance imaging (MRI) of sacroiliac joints and left heel supported bilateral chronic sacroiliitis and also revealed plantar fasciitis (Figure 2). MRI of lumbar vertebra revealed increased signal and bone marrow edema at lower spine (Figure 3).

Figure 1. X-ray of sacroiliac joint was showed bilateral sacroiliac joint narrowing, with erosions and sclerosis

Figure 2. T2-weighted magnetic resonance imaging of sacroiliac joints supported bilateral chronic sacroiliitis

Figure 3. Magnetic resonance imaging of lumbar vertebra revealed increased signal and bone marrow edema at lower spine

Discussion

FMF is autosomal, recessively inherited autoinflammatory disease, characterized by recurrent crises of peritonitis, pleuritis and arthritis usually with fever (1). The prevalence of the disease in Turkey is 1/1075 while the prevalence in Central Anatolia is 1/395 (7).

FMF is an autosomal recessive disease caused by mutation(s) in a specific gene had defined that FMF associated with missense mutation in *MEFV* gene which is located on the short arm of chromosome 16p13.3, exon 10 (the most affected exon) in 1992 (8).

MEFV gene product a protein known as pyrin or marenostin. Pyrin regulates the inflammation reaction in the granulocytes. Defective pyrin causes

excessive migration of leukocytes to the serosal organs, improper and longstanding response to inflammatory stimuli (9).

Articular involvement is observed in nearly 75% of patients which is more like transient and non-erosive arthritis of the large joints of the lower extremities involvement. Chronic arthritis can be seen in 5% of patients (10,11). Rarely, it is known to have a association with spondyloarthritis, some FMF patients have sacroiliitis, enthesitis, inflammatory back pain who are mostly HLA-B27 negative (12).

In a study conducted in Israel, Langevitz et al. (5) reported that sacroiliitis was seen only 11 patients (0.4%) in 3000 FMF patients with chronic arthritis. However, sacroiliitis had not been evaluated by MRI. In our case, we assessed the sacroiliac joints with X-ray and MRI. FMF patients with sacroiliitis were reported to be common in Turkey than the other populations (5,12).

The *M694V* mutation at the patients with FMF is the most frequent mutation in the some ethnic groups like Armenians and Turks. In our country the most common mutations are *M694V*, *M680I*, *E148Q* and *V726A*. In 43.5% of patients with FMF was detected *M694V* mutation in Turkey (13). Dewalle et al. (14) has shown that *M694V* homozygous genotype caused starting disease at an earlier age, higher prevalence of pleuritis, the increasing incidence of arthritis and amyloidosis whom taking colchicine therapy irregularly. This genotype was associated with more severe disease forms (14,15).

In a study conducted in Turkey related with FMF patients, arthritis was detected 71.4% of patients with homozygous *M694V* mutation while it was 29.4% of patients with heterozygous *M694V* mutation (13).

MEFV gene can be seen in other rheumatic diseases as Behcet's disease and inflammatory bowel disease (16). Yigit et al. (17) showed that *MEFV* gene mutations are closely related to improve AS. In recent years, patient with heterozygous *M694V* mutation was found to be associated with SpA in FMF patients.

Also the presence of the *HLA-B27* may be associated with poor prognostic factor for FMF patients related with SpA. *HLA-B27* positivity in FMF patients with spinal involvement has indicated that occurring incidentally with AS or a severe form of FMF associated with SpA (18).

Enthesitis is an inflammation which occurs at the site of the attachment a tendon or ligament to a bone and is the pathologic feature of SpA. Most frequently symptom is the heel pain (19).

HLA-B27 is also closely associated with enthesitis, in the same way some recent studies has shown the *M694V* mutation is thought to be related with the enthesitis in the FMF population (6,20).

In our case, although the patient had inflammatory low back pain, limitations in lumbar motion and enthesitis, he was *HLA-B27* negative and does not have characteristic radiographic features like syndesmophytosis, bamboo spine and square vertebra as AS in his lumbar radiography. Due to his present symptoms and family history we could not defined that case as primer AS. His sacroiliac joint MRI and clinical findings satisfied The Assessment of SpondyloArthritis international Society classification criteria. So we described this case as FMF associated with spondyloarthritis.

Borman et al. (10) reported two cases of FMF-related SpA whom were *M694V* homozygous mutation carrier and had sacroiliitis. One of the patients had heel pain (10). Our case is separated from this case due to *M694V* heterozygous mutation carrier and presence of sacroiliitis. Distinct from this case, his five children had similar symptoms like their father in our case. In this respect our case is similar to Erten et al.'s (21) case. We have reported a second case of FMF with heterozygous *M694V* mutation association with SpA.

Conclusion

FMF is an important common rheumatic disease in our country. Apart from the typical serositis symptoms of disease, sacroiliitis and enthesitis are rarely seen in FMF. The presence of these findings should be kept in mind FMF and SpA combination. Our study can support the hypothesis of heterozygous *M694V* mutation can be connect between the two disease. Further investigations are required to demonstrate common etiopathogenesis of these diseases.

Ethics

Informed Consent: Informed consent was obtained from all patients for being included in the study.

Peer-review: Internally peer-reviewed.

Yazarlık Katkıları

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References

1. Onen F. Familial Mediterranean fever. *Rheumatol Int* 2006; 26: 489-96.
2. Gershoni-Baruch R, Shinawi M, Leah K, Badarnah K, Brik R. Familial Mediterranean fever: prevalence, penetrance and genetic drift. *Eur J Hum Genet* 2001; 8: 634-7.
3. Ben-Chetrit E, Levy M. Familial Mediterranean fever. *Lancet* 1998; 351: 659-64.
4. Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009; 68: ii1-44.
5. Langevitz P, Livneh A, Zemer D, Shemer J, Pras M. Seronegative spondyloarthropathy in familial Mediterranean fever. *Semin Arthritis Rheum* 1997; 27: 67-72.
6. Tufan A, Mercan R, Tezcan ME, Kaya A, Bitik B, Ozturk MA, et al. Enthesopathy in patients with familial Mediterranean fever: increased prevalence in *M694 V* variant. *Rheumatol Int* 2013; 33: 1933-7.
7. Ozen S, Karaaslan Y, Ozdemir O, Saatci U, Bakkaloglu A, Koroglu E, et al. Prevalence of juvenile chronic arthritis and familial Mediterranean fever in Turkey: a field study. *J Rheumatol* 1998; 25: 2445-9.
8. Ben-Chetrit E, Touitou I. Familial mediterranean Fever in the world. *Arthritis Rheum* 2009; 61: 1447-53.
9. Yamazaki K, Yamazaki T, Masumoto J, Suzuki A, Yazaki M, Agematsu K. [Familial Mediterranean fever as representative autoinflammatory disease]. *Rinsho Byori* 2009; 57: 371-81.
10. Borman P, Gokoglu F, Tasbas O, Yilmaz M, Yorgancioglu ZR. Familial Mediterranean fever-related spondyloarthropathy. *Singapore Med J* 2009; 50: e116-9.
11. Estublier C, Stankovic Stojanovic K, Bergerot JF, Broussolle C, Seve P. Myositis in a patient with familial Mediterranean fever and spondyloarthritis successfully treated with anakinra. *Joint Bone Spine* 2013; 80: 645-9.
12. Kasifoglu T, Calisir C, Cansu DU, Korkmaz C. The frequency of sacroiliitis in familial Mediterranean fever and the role of *HLA-B27* and *MEFV* mutations in the development of sacroiliitis. *Clin Rheumatol* 2009; 28: 41-6.

13. Akar N, Misiroglu M, Yalcinkaya F, Akar E, Cakar N, Tumer N, et al. MEFV mutations in Turkish patients suffering from Familial Mediterranean Fever. *Hum Mutat* 2000; 15: 118-9.
14. Dewalle M, Domingo C, Rozenbaum M, Ben-Chetrit E, Cattani D, Bernot A, et al. Phenotype-genotype correlation in Jewish patients suffering from familial Mediterranean fever (FMF). *Eur J Hum Genet* 1998; 6: 95-7.
15. Orbach H, Ben-Chetrit E. Familial mediterranean fever - a review and update. *Minerva Med* 2001; 92: 421-30.
16. Gül A. Behçet's disease as an autoinflammatory disorder. *Curr Drug Targets Inflamm Allergy* 2005; 4: 81-3.
17. Yigit S, Inanir A, Karakus N, Kesici E, Bozkurt N. Common Mediterranean fever (MEFV) gene mutations associated with ankylosing spondylitis in Turkish population. *Dis Markers* 2012; 33: 113-8.
18. Maras Y, Akdogan A, Kisacik B, Kilic L, Yilmaz E, Tufan A, et al. MEFV mutation frequency and effect on disease severity in ankylosing spondylitis. *Turk J Med Sci* 2014; 44: 203-7.
19. Balaban B, Yasar E, Ozgul A, Dincer K, Kalyon TA. Sacroiliitis in familial Mediterranean fever and seronegative spondyloarthropathy: importance of differential diagnosis. *Rheumatol Int* 2005; 25: 641-4.
20. Gulhan B, Akkus A, Ozcakar L, Besbas N, Ozen S. Are MEFV mutations susceptibility factors in enthesitis-related arthritis patients in the eastern Mediterranean?. *Clin Exp Rheumatol* 2014; 32: 160-4.
21. Erten S, Erzurum C, Altunoglu A. Three family members with familial Mediterranean fever carrying the M694V mutation showed different clinical presentations. *Intern Med* 2012; 51: 1765-8.