



## AREL ÜNİVERSİTESİ SAĞLIK BİLİMLERİ FAKÜLTESİ DERGİSİ

JOURNAL OF FACULTY OF HEALTH SCIENCES AREL UNIVERSITY

Web sayfası (Homepage): <https://sbfdergisi.arel.edu.tr>



Olgu Sunumu

### Multiple Sclerosis in a Patient with Familial Mediterranean Fever and Psoriasis: a Case Report and Review of the Literature

Songül İnce<sup>1</sup>, Gökçe Zeytin Demiral<sup>2</sup>, Selin Betaş Akın<sup>3\*</sup>, Ülkü Türk Börü<sup>4</sup>

<sup>1</sup>Department of Physical Medicine and Rehabilitation, School of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey  
e-mail: songulince07@gmail.com  
Orcid: <https://orcid.org/0000-0002-5006-6409>

<sup>2</sup>Department of Neurology, School of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey  
e-mail: gokce\_zeytin@hotmail.com  
Orcid: <https://orcid.org/0000-0002-9635-5804>

<sup>3</sup>Department of Neurology, School of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey  
e-mail: selin\_betas@hotmail.com  
Orcid: [https://orcid.org/\\_0000-0002-7372-2907](https://orcid.org/_0000-0002-7372-2907)

<sup>4</sup>Department of Neurology, School of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey  
e-mail: uturkboru@hotmail.com  
Orcid: <https://orcid.org/0000-0002-0094-5624>

#### Abstract

In patients with FMF, there is a subclinical inflammation even during attack-free periods. This continued inflammation conferred by inflammatory response and the presence of MEFV mutation may predispose patients with FMF to developing other inflammatory disorders. Also, patients with MS are more likely to have other autoimmune disorders particularly prior to the diagnosis of MS. We reported a case of multiple sclerosis developing in a patient had the homozygous M694V gene mutation and diagnosed with fmf and psoriasis(PsO). The patient had been FMF attack free for the past two years. The patient was no attack at the time of admission. After FMF diagnosed in patient, psoriasis developed 2 years later and multiple sclerosis 10 years later.

**Keywords:** Demyelinating disease, MEFV mutation, Multiple sclerosis; Familial mediterranean fever, Psoriasis;

### Ailesel Akdeniz Ateşi ve Psoriazisi Olan Bir Hastada Multipl Skleroz: Bir Olgu Sunumu ve Literatürün Gözden Geçirilmesi

#### Özet

FMF hastalarında ataksız dönemlerde bile subklinik inflamasyon vardır. İnflamatuvar yanıtın neden olduğu bu sürekli enflamasyon ve MEFV mutasyonunun varlığı, FMF'li hastaları başka enflamatuvar bozukluklar geliştirmeye yatkın hale getirebilir. Ayrıca MS'li hastalarda özellikle MS tanısından önce başka otoimmün hastalıklara sahip olma olasılığı daha yüksektir. Homozigot M694V gen mutasyonu olan, FMF ve psoriazis(PsO) tanısı almış bir hastada gelişen multipl skleroz olgusunu bildirdik. Hasta son iki yıldır FMF atağı geçiriyordu. Hastanın başvuru anında atak yoktu. Hastada FMF tanısı konulduktan 2 yıl sonra psoriazis, 10 yıl sonra da multipl skleroz gelişti.

**Anahtar kelimeler:** Demiyelinizan hastalık, MEFV mutasyonu, Multipl skleroz, Psöriazis

**Başvuru:** 31 Ocak 2023 **Kabul:** 3 Nisan 2023

\***Sorumlu yazar:** selin\_betas@hotmail.com

Department of Neurology, School of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey

**Dergi maili:** sbfdergisi@arel.edu.tr

**Dergi kısaltmaları:** Arel Ü. Sağ. Bil. Fak. Derg.  
J. Fac. Health Sci. Arel U.

## 1. INTRODUCTION

Familial Mediterranean Fever (FMF) is a recessive disorder characterized by episodes of fever with serositis or synovitis (Unal et al., 2010). FMF possesses the most common five gene mutations and these mutations include V726A, M694V, M694I, M680I and E148Q (Unal et al., 2010). These mutations account for 74% of all FMF illnesses (Unal et al. 2010). Neurological involvement during the course of FMF, such as aseptic meningitis, pseudotumor cerebri, and demyelinating lesions have been previously reported (Salehzadeh et al. 2020). Various studies have reported the relationship between the MEFV mutation and the development of demyelinating lesions and autoinflammatory diseases (Salehzadeh et al., 2020; Akman et al., 2006, Kalyoncu et al., 2010; Guncan et al., 2016). Nevertheless, coexistence of MS with rheumatic disorders such as FMF has also been rarely reported especially in MS (Salehzadeh et al. 2020). MS is chronic inflammatory disease of the CNS. MS disease must be differentiated from CNS manifestations of other systemic autoimmune diseases such as FMF (Trest et al., 2010; Langer et al., 2010). Coexistence of MS in patients FMF and psoriasis is a rare condition (Salehzadeh et al., 2020; Erden et al., 2018). We reported a case of MS developing in a patient had the homozygous M694V gene mutation and diagnosed with FMF and psoriasis. As far as we know, there are no case reports regarding the coexistence of these 3 diseases.

## 2. CASE

A 32 year old male patient was admitted to our outpatient clinic with numbness in the right foot weakness, and difficulty walking, all of which had started a week prior. He had also experienced similar symptoms 1,5 years prior. However, his symptoms improved without medical treatment.

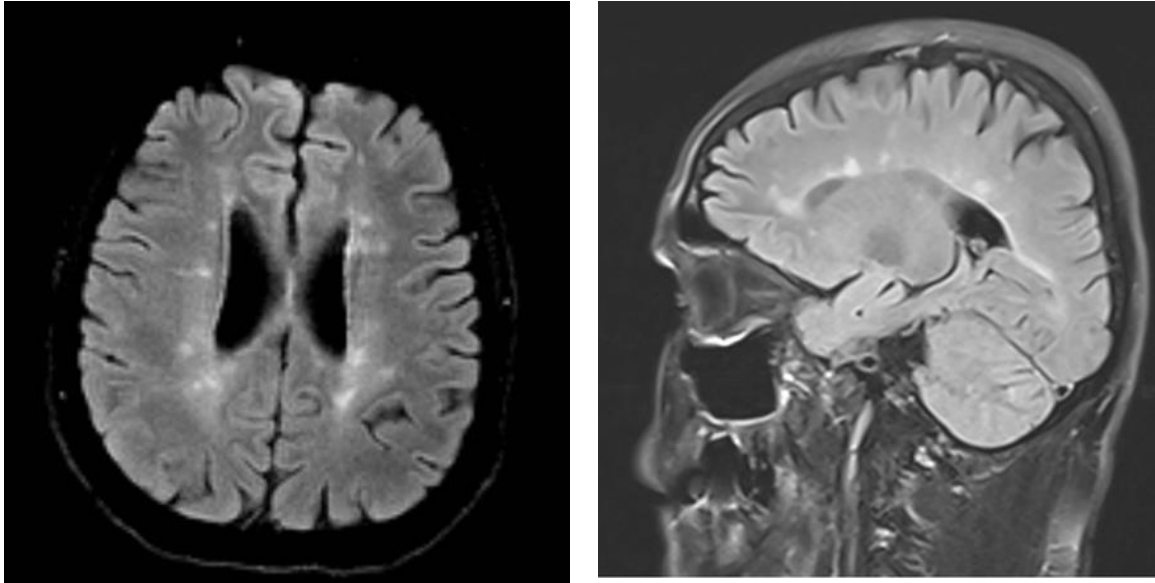
He was diagnosed with FMF 10 years prior, and psoriasis 8 years prior, and has been prescribed colchicine 0.5 mg 2 x 1 for the treatment of FMF for the past 10 years, and topical cortisone creams for the treatment of psoriatic lesions for the past 8 years. The patient had the M694V homozygote gene mutation. Up until two years ago, he suffered abdominal pain and fever attacks twice a year. He had been FMF attack free for the past two years. He was attack free on admission to the clinic.

On physical examination; he had psoriatic lesions on the extensor surface of the elbow and knee. Muscle strength in the distal of the right lower extremity was 3/5 and the proximal 5/5. Muscle strength in the upper and lower extremities were normal. On the dorsal surface of the right ankle, patchy hypoesthesia was present. It did not conform to any dermatomal distributions nor innervation area of the peripheral nerve. Vibration sensation was moderately reduced in the lower extremities and muscle stretch reflexes were increased at the lower extremities. Babinski sign was bilateral pozitif.

Laboratory findings: the white blood cell (WBC) count was normal (9,62 10<sup>3</sup>/μL N: 4-10.10<sup>3</sup>/μL). CRP: 3.4 mg/dl (ref 0-0.5) and Fibrinogen 423 mg/dl (ref 200-400 mg/dl) were slightly elevated. Erythrocyte sedimentation rate (ESR): 9 mm/h was normal. Anti-Borrelia burgdorferi ELISA serology and Anti-Brucella ELISA serology were negative. Cerebrospinal protein 50 mg / dl was slightly elevated, glucose levels were normal and acellular. There were oligoclonal IgG bands in CSF and type 2 was positive, aquaporin-4 was negative.

Cranial MRI (T2-FLAIR) and thoracic MRI T2-weighted showed hyperintense multiple lesions (Figures 1. and 2). On the thoracic and cranial lesions, there were no contrast enhancements. Electrophysiological examinations were normal.

The patient was diagnosed with multiple sclerosis, and his symptoms improved after 7 rounds of IVMP (Intravenous pulse methylprednisolone) pulse therapy.



**Figure 1.** Cranial MRI (T2-FLAIR) axial (a) and sagittal (b) view showing multiple hyperintense lesions extending perpendicular to the corpus callosum in the periventricular white matter.



**Figure 2.** Thoracal (th) MRI (T2 weighted) showing hyperintense lesions at th7-8 and th8-9.

### 3. DISCUSSION

This case report is the first report of the extremely rare coexistence of three diseases; a case of MS developing in a patient diagnosed with psoriasis and FMF.

In a systematic review investigating the association of MS and FMF, %0.2 of 1763 MS patients had the homozygous MEFV gene mutation and %14 had the heterozygous MEFV gene mutation (Elhani et al., 2021). Akman et al. (2006) reported that the estimated prevalence of FMF in MS was increased 4 times (Akman et al., 2006, Korkmaz et al., 2022). They also reported 9 cases with demyelinating disease among 2000 FMF patients. This finding shows 10 times the expected prevalence of MS among FMF patients (Akman et al., 2006; Korkmaz et al., 2022). In a Turkish MS study investigating the frequency of MEFV mutations in MS patients, MEFV gene mutation was detected in 20 (%38) of 53 MS patients and 7 (%11) of 66 healthy infants. The results of this study showed that the frequency of MEFV gene mutations in MS patients was higher (Unal et al., 2010).

On the other hand, the prevalence of psoriasis in the normal Turkish population was %0.42, and in a study by Erden A. et al., the frequency of psoriasis in FMF patients was found to be %3.7 (Erden et al., 2018). In another one study, the frequency of psoriasis in FMF patients was found to be %1.6, and it was reported to be more common than in the general population (Atas et al. 2020).

There are also studies on the link between PsO and MS (Kaiser et al., 2019). In a study conducted in patients with psoriasis in Denmark, the MS incidence rates in mild and severe psoriasis patients were %3.22 and %4.55, respectively, while the MS incidence rate in the control group was %1.78 (Kaiser et al. 2019; Egeberg et al., 2016). Avi Fellner et al. found psoriasis in MS patients with a frequency of %4.2 compared to the control group (Fellner et al., 2014).

As a result of the MEVF gene mutation, pyrin causes the secretion and release of the proinflammatory cytokine il-1beta (Korkmaz et al., 2022). IL-1 $\beta$  has an important role in the pathogenesis of autoinflammatory disorders and demyelinating lesions (Ashida et al., 2016). In recent studies, it has been shown that IL-1 has an essential role in signaling early T helper 17 (Th17) differentiation in vitro and in vivo (Erden et al., 2018). The inflammatory response in PsO is promoted by Th17 cells, and similarly, CNS infiltration of Th17 cells with the production of IL-17 occurs in MS patients (Kaiser et al., 2019).

In our patient had the M694V homozygous gene mutation, and there was subclinical inflammation. Because, he had been FMF attack free for a long time, and he was attack free on admission to the clinic. The patient, psoriasis had been developed 2 years and MS 10 years later, after FMF diagnosis.

In conclusion, in patients with FMF, there is a subclinical inflammation even during attack-free periods. This continued inflammation conferred by inflammatory response and the presence of MEVF mutation may predispose patients with FMF to developing other inflammatory disorders. Physicians caring for FMF patients should remain alert to the possible development of a second AID (autoinflammatory diseases) during follow up. Also, patients with MS are more likely to have other autoimmune disorders particularly prior to the diagnosis of MS.

### Authors' Contributions

All authors contributed to the revision and approval of the manuscript.

### Conflict of Interest and Financial Support

There is no conflict of interest regarding this article. No financial resource has been used for this article.

### Informed Consent

Written informed consent was obtained from the patient for the anonymized information to be published in this article.

### References

- Akman, D.G., Gül, A., Gürol, E., Özdoğan, H., Bahar, S., Oge, A.E., Gurvit, H., Saruhan, D.G., Yazıcı, H. and Eraksoy, M. (2006). Inflammatory/demyelinating central nervous system involvement in familial Mediterranean fever (FMF): coincidence or association? *Journal of Neurology*, 253,928-934.
- Ashida, M., Koike, Y., Kuwatsuka, S., Ichinose, K., Migita, K., Sano, S. and Utani, A. (2016). Psoriasis-like lesions in a patient with familial Mediterranean fever. *The Journal of Dermatology*, 43(3), 314-7.
- Atas, N., Armagan, B., Bodakci, E., Satis, H., Sari, A., Bilge, N.S.Y., Salman, B.Y., Yardimci, K.G., Babaoglu, H., Guler, A.A., Karadeniz, H., Kilic, L., Ozturk, M.A., Goker, B., Haznedaroglu, S., Kalyoncu, U., Kasifoglu, T. and Tufan, A. (2020). Familial Mediterranean fever is associated with a wide spectrum of inflammatory disorders: Results from a large cohort study. *Rheumatology International*, 40, 41-48.

- Egeberg, A., Mallbris, L., Gislason, G.H., Skov, L. and Hansen, P.R. (2016). Risk of multiple sclerosis in patients with psoriasis: a Danish nationwide cohort study. *Journal of Investigative Dermatology*, 136(1),93–98.
- Elhani, I., Dumont, A., Vergneault, H., Ardois, S., Le Besnerais, M., Levesque, H., Ouallet, J.C., Savey, L., Aouba, A., Amslem, S., Giurgea, I., Capron, J., Grateau, G. and Laviaille, G.S. (2021). Association between familial Mediterranean fever and multiple sclerosis: A case series from the JIR cohort and systematic literature review. *Multiple Sclerosis and Related Disorders*, 50,102834
- Erden, A., Batu, E.D., Seyhoğlu, E., Sari, A., Sönmez, H.E., Armagan, B., Demir, S., Bilgin, E., Kilic, L., Karadag, O., Akdogan, A., Bilginer, Y., Ertenli, İ., Kiraz, S., Bilgen, A.S. and Kalyoncu, U. (2018). Increased psoriasis frequency in patients with familial Mediterranean fever. *Upsala Journal of Medical Science*, 123(1), 57-61.
- Fellner, A., Dano, M., Regev, K., Mosek, A. and Karni, A. (2014). Multiple sclerosis is associated with psoriasis. A case-control study. *Journal of The Neurological Science*, 338(1-2), 226-228.
- Güncan, S., Bilge, N.Ş., Cansu, D.Ü., Kaşifoğlu, T. and Korkmaz, C. (2016). The role of MEFV mutations in the concurrent disorders observed in patients with familial Mediterranean fever. *European Journal of Rheumatology*, 3(3), 118-121.
- Kaiser, S.A.S., Homan, K.B. and Mansouri, B. (2019) A narrative review of psoriasis and multiple sclerosis: links and risks. *Psoriasis (Auckl)*, 22(9),81-90.
- Kalyoncu, U., Eker, A., Oguz, K.K., Kurne, A., Kalan, I., Topcuoglu, A.M., Anlar, B., Bilginer, Y., Arıcı, M., Yılmaz, E., Kiraz, S., Calguneri, M. and Karabudak, R. (2010). Familial Mediterranean fever and central nervous system involvement: A case series. *Medicine (Baltimore)*, 89(2):75-84.
- Korkmaz, C., Üsküdar, C.D. and Kabay, S.C. (2022). Familial coexistence of demyelinating diseases and familial Mediterranean fever. *Rheumatology International*, 42(1), 167-173.
- Langer, G.A., Albers, K., Van Den Eeden, S. and Nelson, L. (2010), Autoimmune diseases prior to the diagnosis of multiple sclerosis: A population-based case-control study. *Multiple Sclerosis Journal*, 16(7),855-861.
- Salehzadeh, F. and Enteshari, M.A. (2020). Coexisting diseases in patients with familial mediterranean fever. *Open Access Rheumatology*, 12, 65-71.
- Trebst, C., Kümpfel, T. (2010) Neuroimmunologie und Rheumatologie: Schnittmengen und Differenzialdiagnosen. *Der Nervenarzt*, 89, 1095-1105.
- Unal, A., Dursun, A., Emre, U., Tascilar, N.F. and Ankarali, H. (2010). Evaluation of common mutations in the Mediterranean fever gene in multiple sclerosis patients, is it a susceptibility gene? *Journal of the Neurological Science*, 294(1-2), 38-42.