

Case Report

Concurrent demyelinating central nervous system involvement in a case of Familial Mediterranean Fever with the M694V mutation

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Abstract. Familial Mediterranean Fever (FMF) is a hereditary disease seen mainly around the Mediterranean. The most common mutations are M694V, M680I, V726A and E148. Neurological findings and magnetic resonance imaging (MRI) abnormalities resembling multiple sclerosis have been reported in a few cases. We present a case where an M694V mutation was found together with familial Mediterranean fever and multiple sclerosis-type demyelinating disease as this combination is rarely seen.

Key words: Familial Mediterranean Fever, M694V mutation, demyelinating disease

1. Introduction

Familial Mediterranean Fever (FMF) is a hereditary disease seen mainly around the Mediterranean and mostly affecting non-Ashkenazi Jews, Arabs, Turks and Armenians. The most common mutations are M694V, M680I, V726A and E148Q (1). It can also be seen sporadically (2). Although the prevalence of FMF has previously been reported as 0.1% in Turkey (3,4), it may be as high as 1/395 in central Anatolia (1). A recent study from northern Turkey has reported an FMF prevalence of 1/123 (5). It is an autosomal recessive disease characterized by recurrent attacks of fever and serositis. Central nervous system (CNS) signs are very rare and uncertain (6). These signs may be pseudotumor cerebri, optic neuritis, the CNS complications of vasculitis such as polyarteritis nodosa, secondary hypercoagulopathy due to renal amyloidosis, headaches, nonspecific electroencephalography (EEG) changes that appear during the attacks, recurrent aseptic

meningitis, amyloid ophthalmoplegia and ischemic stroke developing because of coincidental problems (6). Neurological findings and magnetic resonance imaging (MRI) abnormalities resembling multiple sclerosis have been reported in a few cases (6) (7) (8).

We present a case where an M694V mutation was found together with familial Mediterranean fever and multiple sclerosis-type demyelinating disease as this combination is rare and we also quickly review the genetic aspect of the disease.

2. Case report

A 42-year-old female had been followed-up for FMF for approximately 25 years and was receiving colchicine treatment. Her brother had also been diagnosed with FMF and was using colchicine. The patient described one poorly defined visual loss attack approximately 4 years ago and two attacks of almost complete loss of strength in both legs together with urinary incontinence approximately 1 year ago. Pathological findings during the neurological examination were motor dysphasia, limitation of eye movement in all directions, paraparesis more pronounced in the right lower extremity, bilateral deep tendon reflex hyperactivity that was more pronounced in the lower extremities, bilateral positive Babinski sign and right positive Achilles clonus. Cranial and spinal MRI showed round or

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oval multiple nodular demyelinating lesions in bilateral periventricular white matter, with the largest sized 15 mm in diameter in the left parietal lobe, located perpendicular to the ventricular plane, hypointense on T1A sequences and hyperintense on T2A sequences with no signal change following IV Gd injection (Figure 1 and 2). There were also lesions with similar

characteristics in the cervical spinal cord (Figure 3) and the medulla oblongata. The patient had presented at our clinic approximately 1 year after the attack and the visual potentials revealed no significant pathology. FMF-related MEFV gene mutations were investigated and the M694V mutation was found.

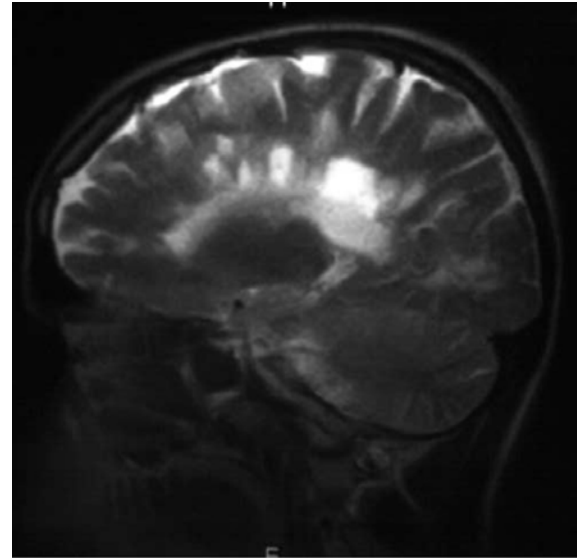
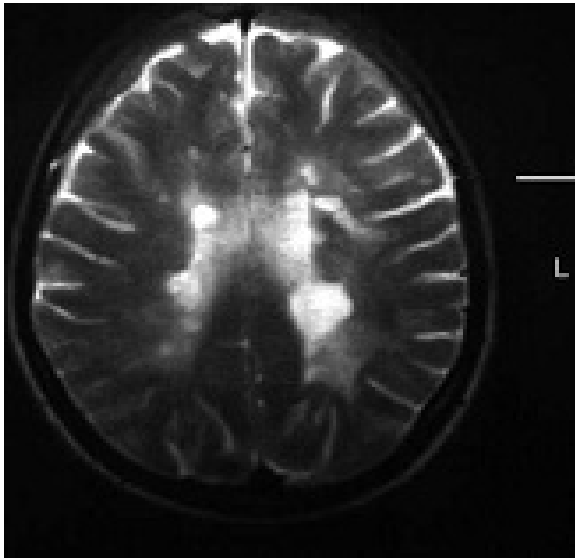


Fig. 1 and 2. Demyelinating lesions in bilateral periventricular white matter with no signal change following IV Gd injection.

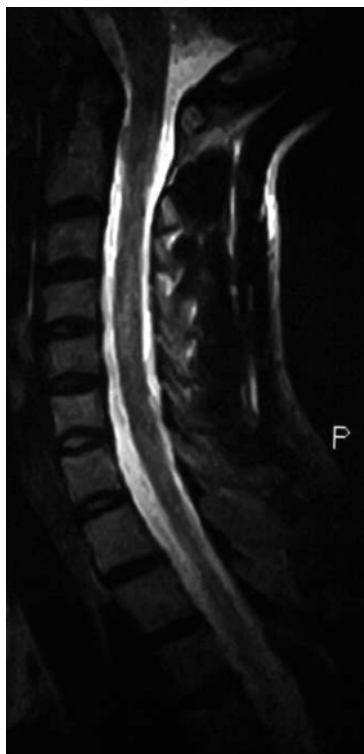


Fig. 3. Demyelinating lesions in the cervical spinal cord.

3. Discussion

Familial Mediterranean Fever can rarely cause neurological symptoms. However, various signs related to neurological involvement have been reported in FMF cases at different rates in the literature (6). The pathological finding in familial Mediterranean fever is nonspecific acute inflammation. Amyloid accumulates in the venule subendothelium and arteriole intima and media in all major organs. It is commonly believed that the liver, heart and brain are protected (6). Amyloidosis is a common complication of FMF and may lead to hypercoagulability and subsequent stroke. Polyarteritis nodosa or related vasculitis may be associated with FMF and cause neurological complications (9).

There is limited data available on the concurrence of FMF and MS-type lesions. Topcuoglu et al. (6) have reported MS-like white matter lesions in the brain in 3 FMF cases. Ugurlu et al. (8) have also recently reported a male FMF case with left lower extremity numbness and ataxia and an MS-like plaque similar to our case on spinal and cranial MRI. Guinet et al. (7) have defined relapsing-remitting

neurological findings in an FMF case whose sibling also had MS.

Many genetic studies have been performed in countries with a high incidence of FMF to understand its genetic features. The four most common mutations in Turkish FMF patients are M694V, M680I, V726A and E148Q. The M694V incidence is 39.1-70% while the rates are 4.9-14.4% for M680I, 7.3-11.4% for V726A and 1.3-5.4% for E148Q (1). Our case had M694V, the most common mutation in our country.

The concurrence of Familial Mediterranean Fever and multiple sclerosis-like signs in the same patient may be coincidental or related to an unknown pathophysiological relation with a genetic basis.

Akman-Demir et al. (9) have reported 12 FMF cases among 2800 patients being followed-up with a diagnosis of MS. Eight of these FMF patients had the FMF-associated mutations of M694V, V726A and M680I. Shinar et al. (10) have investigated the common FMF gene mutations associated with rapid progression to disability in their study on Ashkenazi Jews and concluded that non-Ashkenazi MS patients carrying one mutated MEFV gene, particularly M694V, expressed rapid progression to disability. They state that the expressed mutation may increase inflammatory damage inflicted by autoimmune responses.

Familial Mediterranean Fever is not an autoimmune disease but is commonly seen together with various vasculitis such as poliarteritis nodosa and Henoch-Schönlein purpura. Behçet's disease (BD), another common disease in our country, is also a vasculitis that can be seen in the various ethnic groups affected by FMF. However, there have been only a few studies on the relation between FMF and Behçet's disease (11). Schwartz et al. (11) have found 39 cases with FMF and BD among the 4000 patients being followed-up at their FMF clinic. These patients were from 31 FMF-BD families with 280 members. This study noted a possible relation between FMF and BD and indicated that the risk of BD and FMF concurrence in the same person was higher than expected. Livneh et al. (12) studied the incidence of the 4 most common FMF mutations (M694V, V726A, M680I and E148Q) and found a homozygous or heterozygous M694V mutation in most patients. Rabinovich et al. (13) performed an MEFV analysis in 54 BD patients and found M694V, V726A and E148Q to be the most common mutations. Imirzalioglu et al. (14) compared 42 BD patients with control subjects and found the most common gene mutations to be M694V, V726A, E148Q and M680I MEFV.

The similarity of the clinical and laboratory findings of Behçet's disease and multiple sclerosis can sometimes make it difficult to differentiate the two conditions. This prevents us from stating that the central nervous system findings of our case were due to an inflammatory/demyelinating disorder. However, the common genetic features of these diseases indicate that multiple sclerosis, Behçet's disease and FMF may be seen in the same patient.

A prospective study investigating neurological involvement in a small group of 17 FMF patients, conducted by the group that originally described MS-like cases, failed to show any CNS demyelination (15). However, it is important to emphasize the neurological findings of FMF so that internists who are the physicians that see these patients most commonly and neurology outpatient departments can follow-up these patients properly. We do not have adequate data on the incidence of asymptomatic neurological involvement in the FMF group. Large-scale genetic studies that would enable understanding the genetic basis of the relation between multiple sclerosis, Behçet's disease and FMF are also needed.

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