

Co-existence of familial Mediterranean fever and multiple sclerosis in two patients

Ceylan G¹, Erten S², Ercan K³

ACTA REUMATOL PORT. 2014;39:342-344

ABSTRACT

Two female patients, aged 23 and 25 years-old diagnosed with familial Mediterranean fever (FMF) were presented with ataxia and headache. Multiple sclerosis plaques were detected in their spinal and cranial MRI and diagnosis of multiple sclerosis was established. Genetic analysis demonstrated M694 V mutation (one homozygous and the other heterozygous) in both of the patients. Although it is quite rare, coexistence of familial Mediterranean fever and multiple sclerosis should be kept in the mind.

Keywords: Familial Mediterranean fever; Multiple Sclerosis; Genetics

INTRODUCTION

Familial Mediterranean fever (FMF) (OMIM #249100) is an autosomal recessive disorder characterized by recurrent attacks of pleuritis, febrile peritonitis and synovitis. It affects mainly Turks, Arabs, Armenians and non-Ashkenazi Jews¹. Mediterranean fever (MEFV) gene consists of 10 exons and encodes a 781 amino acid protein called pyrin which is expressed in polymorphonuclear cells, cytokine activated monocytes, dendritic cells and synovial fibroblasts^{2,3}. Mutations interfere with the role of the pyrin domain, allowing an uninterrupted inflammatory cascade⁴.

Multiple sclerosis (MS) is a chronic inflammatory brain and spinal cord disease characterised by inflammation, demyelination and axonal degeneration and

caused by complex interactions of both environmental and genetic factors. IL-1 β , which is expressed by microglial cells and infiltrating monocyte/macrophages in white matter and around the lesions is likely to play a part in MS pathogenesis. Functional studies suggest that pyrin is implicated in the maturation and secretion of IL-1 and mononuclear cells of FMF patients secrete increased levels of IL-1 β which is a major mediator of fever and systemic inflammation⁵.

Here, we presented two cases of women with FMF and MS.

CASE REPORT

Case 1: A 23-year-old woman was admitted to our hospital 4 years ago with recurrent attacks of abdominal pain, fever, arthralgia and diarrhea. At that time she has also complained about recurrent chest pain and oral aphthous ulcers. C-reactive protein (CRP) was 78.9 mg/L(0-4,9) erythrocyte sedimentation rate (ESR) was 26 and fibrinogen was 832 mg/dL (150-400) during acute attack. Pathergy test was negative. Cardiovascular and respiratory system examinations of the patient were normal. In her family history, her brother has also been learned to have FMF. Genetic evaluation of the patient demonstrated heterozygous M694V mutation and HLA B27 test was negative. Therefore, colchicine 1.5 mg/day was started. Two years later, she started to complain about vertigo, numbness of left arm, lower extremity pain and light-headedness. Cervical MRI showed multiple hyperintense signal change lesions compatible with demyelinating plaques in spinal cord at the level of C1, C2, C4, C5 and C6 which were consistent with MS (Figure 1). Oligoclonal IgG was detected in immunofixation electrophoresis of cerebrospinal fluid. Three doses of pulse corticosteroid treatment was given. The patient was recommended to use interferon beta-1b which she did not.

1. Department of Medical Genetics, Ankara Atatürk Education and Research Hospital

2. Department of Rheumatology, Ankara Atatürk Education and Research Hospital

3. Department of Radiology, Ankara Atatürk Education and Research Hospital



FIGURE 1. In cervical sagittal STIR images, hyperintense intramedullary demyelinating plaques in the spinal cord at the level of C1-2 (Case 1)

On follow-up, she developed posterior uveitis. Oral corticosteroid, ciclosporin and azothioprin were added. With these treatment, uveitis of the patient was recovered.

Case 2: A 25-year-old woman was admitted to our hospital because of headache and vertigo. Despite the antidepressant and nonsteroid antiinflammatory therapy (NSAID), she applied again with feelings of pins and needles in her hands, tremor, fainting, left-sided headache and ataxia two months later. In her past-medical history, she was learned to be diagnosed as FMF due to recurrent abdominal pain, fever and arthralgia 19 years ago. She has been using colchicine treatment since then. In neurological examination, hypoesthesia in left side of the body, increased deep tendon reflexes (DTR) was detected. Cranial MRI showed hyperintense signal change lesions compatible with demyelinating plaques bilaterally in periventricular white matter, perpendicular to the ventricular axis (Figure 2). She had also diplopia. She was diagnosed as multiple scler-



FIGURE 2. Periventricular demyelinating plaques in sagittal FLAIR images (Case 2)

rosis, hospitalized and treated with pulse corticosteroid therapy. Interferon beta-1b was added on follow-up.

On follow-up, she was re-admitted with abdominal and back pain. She had elevated acute phase response as fibrinogen 822 mg/dl, ESR 36 mm/h and CRP as 60,9 mg/L during the attack. Sacroiliac magnetic resonance imaging was performed due to inflammatory back pain. Sclerosis and edema of left sacroiliac joint was present. Genetic evaluation demonstrated homozygous M694V mutation. The patient was diagnosed as FMF related spondyloarthritis and colchicine dosage was increased to 2 mg/day and NSAID was added to treatment.

DISCUSSION

The relationship between FMF and MS remains still controversial. In a study by Akman et al, the authors suggested a 4-fold increased rate of FMF among patients with MS. They also reported that the presence of MEFV variations could change the incidence and progression of other inflammatory diseases⁶. Few cases indicating the coexistence of FMF and MS were reported^{7,8,9}. According to Shinar *et al.*, the rate of M694V mutations was not high in patients with MS, but disease could proceed more rapidly in patients with MS carrying one mutant MEFV gene. Therefore, we must

be provident about the prognosis of patients with both MS and FMF⁹. We detected M694V mutation in both of our patients, one of which was heterozygous, but the other was homozygous for this mutation. So, there can be a susceptibility to MS in patients with M694V mutation carriage.

There is no suggested mechanism how the mutated MEFV gene could enhance the progress of neurological disability. One of the possible options is that the mutated MEFV may augment the secretion of oligotoxic and neurotoxic compounds. This can occur by failing to downregulate the inflammatory response of monocytes and activated microglia within the MS brain lesions⁹. Alpaycı *et al.* proposed that the caspase-1 activation and release of IL-1 beta may be a common underlying pathway in the pathogenesis of FMF and MS. Fever, inflammation, endothelial dysfunction, and vasculitis, which occur during the course of FMF may play a key role in the development of demyelination and axonal damage increases. This develops a risk for the development of MS especially during the FMF recurrent attacks⁵.

These two cases are good examples of increased inflammation and increased frequency of autoimmune diseases in FMF. Further studies are necessary to clarify the relationship between autoimmune diseases and the genetic mechanisms.

CORRESPONDENCE TO

Sukran Erten
Atatürk Education and Research Hospital,
Department of Rheumatology, Bilkent/Ankara
E-mail: sukranerten@yahoo.com

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