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Dates: Received: 08 July, 2016; Accepted: 09 September, 2017; Published: 12 September, 2017

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Keywords: Familial mediterranean fever; Fibromyalgia syndrome; MEFV gene

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Case Report

The Coexistence of Familial Mediterranean fever and Fibromyalgia Syndrome: Two Cases Reports

Abstract

Familial Mediterranean Fever (FMF) is an autoinflammatory disease caused by mutations in the MEFV gene and characterized by recurrent fever, polyserositis and arthritis. It is transmitted in an autosomal recessive pattern. FMF has been predominantly found in ethnic groups living around the Mediterranean basin (Jews, Arabs, Turks, and Armenians). Although accompanying inflammatory diseases have been reported in FMF, the coexistence of fibromyalgia syndrome (FMS) is very rare. MEFV gene analysis that the first patient had compound heterozygous mutation (M680I+V726A) and the other patient had heterozygous mutation (M694V). This association will be discussed in this case report.

Introduction

Familial Mediterranean Fever (FMF) is an autosomal recessive disease characterized by recurrent fever, abdominal pain, monoarthritic and/or oligoarthritic arthritis, polyserositis, and erysipelas-like erythema [1]. FMF has been predominantly found in ethnic groups living around the Mediterranean basin (Jews, Arabs, Turks, and Armenians) [1]. The gene responsible for the FMF, called MEFV gene is localized on chromosome 16p13.1. Recently, it was reported that out of over 300 mutations in MEFV gene. The most common mutations are M694V, M680I, V726A and E148Q [2]. MEFV gene encodes pyrin protein that is an important modulator of immunity.

Fibromyalgia syndrome (FMS) is a clinical condition characterized by several symptoms including chronic widespread pain, sleep disturbances, cognitive functional dysregulation and fatigue and has negative effects in patient's life [3]. Its annual prevalence is 1-5%, and 90% of FMS patients are women [4]. Its etiology has not been known clearly, but psychological, neurobiological and environmental factors are considered to play a role in the development of FMS [4]. The coexistence of FMS and FMF was detected into cases that presented to our clinic. This paper discusses these cases.

Case 1

A 35-year-old female patient presented to the polyclinic of Physical Therapy and Rehabilitation with complaints of fatigue and pain on left shoulder. The patient had previously been diagnosed with FMF, and was taking colchicine pills (0.5 mg/

day). The patient was additionally taking amitriptyline 25 mg pills. The patient had MEFV gene M680I+V726A compound heterozygous mutation. The physical examination showed that the patient had pain and tenderness on the left shoulder. There was also tenderness at some points in her body. There was no sign of oral and genital aphtha, eruptions, weight loss, swollen joints or itching. The results of complete blood count and liver function tests were normal. The sedimentation was 76 (normal range 5.1-10.7), and CRP was 200 mg/L (normal range 0-5 mg/L).

Case 2

A 52-year-old female patient who presented to the polyclinic of Physical Therapy and Rehabilitation had complaints of hip and back pain, hand numbness and morning stiffness. She also had urinary complaints. The patient, diagnosed with FMF one and a half year ago, had M694V heterozygous mutation. The patient was taking colchicine pills (0.5 mg/day). The patient also had hypertension and migraine. Tenderness was detected in 10-12 areas in physical examination. She had difficulty in opening and closing her hands. There was no swelling, redness or temperature increase in joints. She had no motor deficit. Deep tendon reflexes were symmetrically normoactive. The patient had signs of depression. Biological and serological tests were performed. The results of complete blood count, liver function and hormone tests were normal. The sedimentation was 12 (normal range, 6.2-13.2), and CRP was 26.7 mg/L (normal range 0-5). The MRI of sacroiliac joint was within the normal range.

Discussion

FMF is a genetic autoinflammatory disease. *MEFV* gene mutations vary according to ethnic origin and geographical region. FMF is 1.2 to 1.5 times more common in men than women [2]. The symptoms of FMF generally appear in early years of life. Researchers have reported various rates of prevalence in the Middle East from 1/100 to 1/2000 [2]. Depending on the ethnic difference, heterozygosity is higher in Turkey. The rate of prevalence and carriage was reported between 1/1000 and 15–34% in Turkey [5].

The majority of mutations that cause FMF occur on exon 10 of the *MEFV* gene. The most common *MEFV* gene mutations in Turkey are M694V, M680I and V726A [2]. The geographic distribution of gene mutations in Turkey is as follows: M694V, V726A, M680I in Southeastern and Central Anatolia; M694V, M680I, V726A, K695R and R761H in the Black Sea region; and M694V, M680I, K695R, V726A, M694I, R761H in the Thrace region of Turkey [6].

There are studies reporting that *MEFV* mutations were associated with some inflammatory diseases, including Behçet's disease, inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, and juvenile rheumatoid arthritis. Pyrin protein mutations are responsible for inflammatory symptoms. In FMF patients, the effusion of neutrophils in serous cavities causes inflammatory attacks, which results in increase in acute phase reactants [1]. Various studies have reported that the levels of interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor- α (TNF- α) increase during and between FMF attacks [7,8].

FMS is a chronic idiopathic condition characterized by muscle pains, and affects women more than men. FMS follows a chronic course. The etiology of the disease is not known clearly; however, cytokines such as interleukin-8 (IL-8), tumor necrosis factor- α (TNF- α), IL-6, IL-4, and IL-10 are considered to play a role in the pathogenesis of the disease and the emergence of clinical findings. Some studies have shown that the blood level of some cytokines increases in FMS patients. Clinical findings suggest that FMS and FMF have some common symptoms, including, chronic pain in lower body, tenderness and widespread pain.

A study focusing on five *MEFV* gene mutations (M694V, M680I, V726A, E148Q and P369S) and one *MEFV* gene variant (R202Q) in Turkish FMS patients found a statistically significant difference between FMS patients and control group [3]. These findings lead us to consider that *MEFV* gene mutations and variants cause susceptibility to the development of FMS.

Two patients that presented to our clinic were considered to have FMS according to 2010 ACR diagnosis criteria. Both patients had *MEFV* gene mutations.

In conclusion, the molecular functional mechanisms of the pyrin has been investigated in several studies. It was suggested that mutant pyrin cannot control active interleukin-1 β production. Therefore, there is a need for further studies to enlighten the molecular pathways related to inflammation in FMF.

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