Musculoskeletal Symptoms in Familial Mediterranean Fever

Zelal Ekinci

Abstract

Familial Mediterranean fever (FMF) is a genetic disease characterized by painful febrile attacks of serositis. One of the most important serosal attacks is monoarthritis. Besides arthritis, many other musculoskeletal manifestations (MSM) have been reported. MSM of FMF could be classified as acute and chronic or protracted. Acute MSM includes joint attacks, muscle attacks and skin attacks. Chronic or prolonged MSM includes protracted arthritis and protracted febrile myalgia (PFM). Recurrent acute monoarthritis is one of the diagnostic criteria included both in Tel Hashomer and Yalcinkaya criteria. Misdiagnosis of this presentation as acute rheumatic fever is possible. Muscle attacks present in different forms; one of them is exertional leg pain and the other is recurrent febrile muscle attacks. Chronic MSM of FMF is rare, but important for differential diagnosis. PFM is an attack lasting 6-8 weeks with debilitating myalgia. Differential diagnosis with polyarthritis nodosa is required. Protracted arthritis affects the hips or the knees and requires corticosteroids or sometimes surgery. Sacroilitis in FMF patients should be evaluated in this group. These MSM presentations of FMF are important in patients who are not yet diagnosed as FMF. Unawareness of these manifestations could cause misdiagnosis and delay.

Key words: Familial Mediterranean fever, musculoskeletal manifestations, arthritis, myalgia, protracted arthritis, protracted febrile myalgia

Introduction

Familial Mediterranean fever (FMF) is a genetic disease characterized by painful febrile attacks of serositis and the development of amyloidosis [1]. Since the disease first described in 1945 and the gene of the disease identified in 1992, some sets of criteria were described for the diagnosis. The most famous of these are Tel Hashomer’s (Table 1) and Yalcikaya’s criteria (Table 2) [2,3]. In the Tel Hashomer’s criteria, diagnosis is based on the major and minor criteria [2].

Typical attacks are defined as recurrent (≥ 3 at the same site), febrile (38 C or more, rectal) and short (lasting 12 hours- 3 days) attacks. Incomplete attacks are defined as painful and recurrent attacks differing from
typical attacks in one or two features. One or more major or two or more minor criteria is required for the diagnosis.

They show that presence of two or more of these five criteria diagnosed FMF with a sensitivity of 86.5% and specificity of 93.6%. As presented in these criteria arthritis is an important manifestation of FMF. However, many other deviational musculoskeletal manifestations (MSM) were commonly reported [4-8]. In the report of Turkish FMF study group 72.1% of patients had MSM and MSM were increased among patients who had more frequent attacks, amyloidosis and poor response to colchicine [9]. The aim of this review is to present MSM of FMF. MSM of FMF could be classified as:

1) Acute MSM: joint attacks, muscle attacks and skin attacks
2) Chronic or prolonged MSM: protracted arthritis and protracted febrile myalgia (PFM).

**Acute MSM**

**Acute joint attacks**

The earliest reviews on the articular manifestations of FMF appeared in the mid-1960s. The classical presentation of acute joint involvement was described as a recurrent monoarticular large joint disease that occurred at an early age [10].The articular involvement in FMF episodes is the second most common symptom and experienced by 75% of patients with FMF [2,11,12]. It presents as an abrupt onset of acute arthritis. It occurs suddenly and may be precipitated by minor trauma or effort such as prolonged walking. Usually fever, redness, warmth, tenderness and swelling are accompanied. The most commonly affected joints are large joints of the legs and usually involvement during attack is monoarticular [11,13]. Acute joint attacks usually last longer than other FMF attacks and subsides gradually, leaving no residual damage [13]. The attacks are commonly in the hip or knee but may occur in ankle, shoulder, temporomandibular joint or sternoclavicular joint, fewer than 5% [11,14]. Evaluation of synovial fluid for differential diagnosis resembles other inflammatory arthritis. It is sterile, but contains neutrophils [2,11,13]. Joint attacks should not be confused with polyarthritis. Polyarthritis usually accompanies acute attacks together with myalgia as constitutional symptoms [2]. Oligoarticular presentation, small joint involvement and migratory arthritis require an effort for differential diagnosis. If the patient fulfills the diagnostic criteria for FMF, this kind of presentation could be sign of a second disease in addition to FMF, such as vasculitis or spondyloarthropathies [2]. In a small percentage of patients’ arthritis of upper extremity joints have been also reported. Other clinical patterns of arthritis in FMF included simultaneous symmetrical two-joint arthritis (15%), symmetrical polyarticular and asymmetrical oligoarticular (6%), asymmetrical oligoarticular acute römatic fever like (3.5%), sacroiliac joint involvement (0.5%) and small joints of the hands and feet (5%) [10,15]. Where FMF is prevalent such as in Turkey, recurrent episodes (≥ 3 attacks) of monoarthritis should be accepted as FMF unless otherwise proven [9,11]. The clinical, ethnic, and genetic features of recurrent monoarthritis of FMF are specific and may separate FMF from other entities with mono-oligoarthritis. In the report of Turkish FMF study group patients with arthritis had younger age of onset, more erysipelas-like erythe-

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<th>Table 1. Tel Hashomer’s criteria</th>
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<td><strong>Major Criteria</strong></td>
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<td>1- Peritonitis,</td>
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<td>2- Pleuritis or pericarditis,</td>
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<td>3- Monoarthritis (hip, knee, ankle),</td>
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<td>4- Fever alone and</td>
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<td>5- Incomplete abdominal attacks.</td>
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<td><strong>Minor Criteria</strong></td>
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<td>1- Incomplete attacks of chest,</td>
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<td>2- Incomplete attacks of joint (joints other than specified in major criteria),</td>
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<td>3- Exertional leg pain and</td>
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<td>4- Favorable response to colchicine.</td>
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<th>Table 2. Yalçınkaya et al’s criteria are proposed for children with FMF [3]</th>
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<tr>
<td><strong>Major Criteria</strong></td>
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<tr>
<td>1- Fever (axillary temperature of &gt;38°C),</td>
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<td>2- Abdominal pain,</td>
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<td>3- Chest pain,</td>
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<td>4- Arthritis (oligoarthritis) and</td>
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<td>5- Family history of FMF.</td>
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ma and more myalgia, and more frequently associated with vasculitis than those without arthritis [9]. Patients with M694V/M694V genotype were found to have earlier age of onset and higher frequencies of arthritis and arthralgia compared with the other groups [11,12,16]. These patients could be misdiagnosed as juvenile idiopathic arthritis or acute rheumatic fever frequently in clinical practice. Pediatricians working in the FMF prevalent regions should be aware that FMF may present with attacks of arthritis and misdiagnosis is possible if they are unaware.

**Muscle attacks**

Myalgia is an incapacitating feature of FMF; however, it was not described in the early case reports and large series. Myalgia is defined as pain and tenderness in the extremities away from the joints, in the absence of joint swelling and signs of underlying osteomyelitis [15]. It was first addressed as a feature of FMF in 1980's [17-19]. With increasing knowledge, leg pain on exertion (exercise-induced myalgia) was considered as one of the diagnostic criteria [2]. It has been reported as 20-25% in patients with FMF [20]. Forms of muscle involvement in FMF could be classified as:

- Febrile muscle attacks (short and protracted: PFM will be described in the section chronic and prolonged manifestations),
- Myalgia in Henoch Schönlein purpura and polyarthritis nodosa
- Exertional leg pain,
- Fibromyalgia,
- Constitutional generalized myalgia,
- Colchicine myopathy

**Exercise induced myalgia** is defined as myalgia with an onset within 6 hours of exercise [15]. It can be precipitated by physical exertion or standing for long periods. Usually the pain is severe and lasts from hours to 1-3 days. The pain usually affects the calf. It is not associated with elevated temperature, usually is not accompanied by objective findings, is severe, and is relieved only by rest. The EMG changes are those of mild inflammatory myopathy. It is the most common form seen in FMF [20].

Spontaneous myalgia is defined as myalgia not related to exercise or any other precipitating factor and presents as febrile muscle attacks. Usually appears in the arms and legs and may be associated with arthritis. The pain is usually mild to moderate and lasts for about 8 hours to 1 day [20].

**Constitutional, generalized myalgia** is another non-specific form of muscle pain. Nearly 30% of patients with FMF suffer from muscle pain and other symptoms of fibromyalgia. Juvenile fibromyalgia syndrome is also reported to be prevalent in children with FMF [21,22]. Muscle enzymes, electromyography and muscle biopsy in these patients were found to be normal.

**Colchicine-induced myopathy** is an important diagnostic consideration, because of continuing colchicine treatment. Elevated muscle enzymes and the myopathic pattern on electromyography are the basic differences for the diagnosis.

**Skin attacks**

The most specific skin manifestation of FMF is febrile erysipelas-like erythema and should be described with MSM. It usually affects the lower extremity, usually between the knee and the ankle or may overlay the dorsum of the foot most commonly unilateral. It may be difficult to separate it from underlying joint attack which sometimes accompanies. It is a warm, red and tender skin patch. It is the only rash typical of FMF. In the largest series of FMF, reported by Turkish FMF study group, the erysipelas-like erythema was 20.9% and significantly more prevalent before the age of 18 years [9,11,16].

**Chronic and prolonged manifestations**

**Protracted arthritis**

Short articular attacks, terminating within two-three days, are the most common, but protracted articular attacks persisting for months or even years have also been described in FMF patients [23-25]. Usually despite recurrent acute joint attacks, the joints remain intact in most cases. In approximately 5% of such patients, protracted arthritis develops [14]. Usually these patients are afebrile. Hips and knees are the most affected joints. It lasts a month or more. Inflammation subsides usually in two weeks but synovial effusion lasts longer. Because of the effusion, range of motion is limited and pain is evident and muscle atrophy may develop [26]. Generally complete recovery is the rule. However joint damage may occur in the hip and rarely in other joints. The hip is the most vulnerable joint and is likely to be affected by the protracted attacks and may result in destruction of the articular cartilage [10]. In the evaluation of 84 pro-
tracted joint attacks it was found that 36 of them were knees and 25 of them were hips [27]. The prognosis is poor in the hip and total hip replacement could be required. Chronic knee involvement is second most prevalent involvement and usually requires synovectomy. Chronic massive knee effusion should remind the diagnosis of FMF. Yalcınkaya et al. reported protracted arthritis of both knees [23]. Corticosteroids and colchicine therapy is not enough for long-lasting cases and synovectomy is usually required [23,26,28]. Temporomandibular and shoulder joints are other reported protracted arthritis of FMF [10]. Chronic inflammation of the sacroiliac joint appears to occur more commonly in FMF patients than in the general population [25]. Langevitz et al proposed that the prevalence of seronegative spondyloarthropathy is 0.4%, with a frequency of 11 in 3000 FMF patients [29]. That means sacroiliitis is seen rarely compared to other MSM. Unilateral or bilateral sacroiliitis, enthesitis, back and neck pain could be present. However these patients are all RF and HLAB27 negative. All published cases with seronegative spondyloarthropathy in FMF are HLAB27 negative and have no significant radiological lumbar spine involvement. It is important to differentiate seronegative spondyloarthropathy of FMF from ankylosing spondylitis for the beginning of colchicine therapy. In other words, in all spondyloarthropathies, FMF should be excluded. A lack of awareness of FMF among patients with sacroiliitis may cause misdiagnosis and delay the early treatment option [25,27]. In Turkish patients the frequency of sacroiliitis seems to be higher than previous reports [30]. If an FMF patient with sacroiliitis has HLAB27 and spinal ankylosis, he must be considered to have concomitant FMF and ankylosing spondylitis.

**PFM:** PFM is a rare and recently well described dramatic pattern of FMF. It was first described by Schwabe et al. during the presentation of 100 cases of FMF in two Armenian patients with FMF in 1974 [31]. They noticed the attacks of fever and severe myalgia lasting 10-21 days. In 1988 Schapira et al described a patient whose only manifestation of FMF was severe myalgia with fever [32]. It was subsided in 3 weeks with steroid therapy. Recently, in 1994; Langevitz et al described 14 FMF patients with severe disabling myalgia accompanied by fever, high erythrocyte sedimentation rate, lasting up to 6 weeks [33]. Transient vasculitic rashes mimicking Henoch Schönlein purpura is reported in some of the PFM cases [33-35]. PFM is assumed to be a vasculitic disorder by some authors [35]. Other vasculitis such as HSP, PAN and Behçet’s Disease have been found in an increased incidence in FMF patients [36]. Increased ASO titers in these patients indicate that Streptococci could be one of the agents inducing PFM in patients with FMF [37]. Normal CPK levels together with findings of inflammatory myopathy on EMG differentiated colchicine myopathy in these patients. It was also shown that treatment with prednisone improved the patient dramatically. They concluded that PFM is an uncommon dramatic manifestation of FMF that may occur despite colchicine therapy and require treatment with steroids [33]. Natural course of disease was observed as 6-8 weeks. Despite steroid therapy debilitating myalgia could persist for 9 weeks [38]. PFM develops usually in patients with known FMF, even under colchicine prophylaxis. Sometimes FMF can be diagnosed with PFM as a first manifestation [37,39-42]. Nineteen case reports or case series have been published describing some features of this syndrome, since the first description of PFM in 1994 [20,34,35,37-53]. Fifteen of these were from Turkey [34,35,37-39,41-50]. PFM as a rare clinical finding (1.2%) were more common in M694V homozygotes [44]. Kaplan et al described a set of criteria for the diagnosis of PFM in a group of children in 2007 [40]. 80% of these 15 children were homozygous for M694V, supporting the findings of previous PFM reports. They decided that there is a strong connection between the M694V mutation and PFM. However there is a report of PFM case homozygous for E148Q [48]. Myalgia is so severe that patients are bedridden or wheelchair. The set of criteria for the diagnosis of PFM [40]:

**Obligatory criteria:**
1. FMF-Prior clinical and/or genetic evidence of FMF or familial history of FMF.
2. Myalgia-Bilateral, of the lower and/or upper limbs, characterized by severe muscle pain and tenderness with physical disability, in the presence of normal muscle enzyme levels.
3. Duration of symptoms-Persistence of the myalgia for ≥ 5 days.

**Supporting criteria:**
1) Homozygocity/hemizygocity for M694V mutation.
2) Elevated levels of inflammation markers: ESR ≥ 80mm/h, CRP ≥ 5mg%.
3) Fever ≥ 38.0°C.

Exclusion criteria: Polyarteritis nodosa (PAN) which is reported to be coincidental with FMF shares same common findings of PFM such as fever of unknown origin, weight loss, severe abdominal pain, hypertension, arthralgia, arthritis, or myalgia. For this reason polyarteritis nodosa should be excluded during differential diagnosis [39].

Conclusion
The importance of MSM of FMF has been better understood in recent decades. FMF is still diagnosed with clinical findings. The widely defined MSM are very important for diagnosis and differential diagnosis of FMF. Pediatricians’ awareness of these symptoms reduces the possibility of misdiagnosis of FMF as acute rromatic fever, juvenile idiopathic arthritis and polyartheritis nodosa and prevents the delay of FMF diagnosis.

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References


