

# Protracted febrile myalgia syndrome in patient with familial mediterranean fever

## Abstract

Familial Mediterranean fever (FMF) is a one of genetically basis auto inflammatory disease characterized by recurrent episodes of fever, serositis & musculoskeletal involvement. Protracted febrile myalgia syndrome (PFMS) is characterized by severe paralyzing myalgia, high fever, abdominal pain, diarrhea, arthritis/arthralgia, and transient vasculitic rashes. We report a 15year-old girl with PFM as non classical presenting symptoms of FMF, and discuss the course of management of this case.

We reviewed the literature and mostly recorded all case reports of PFM affected adolescent and adult patients over the past years to give special prominence to muscle affection in FMF particularly PFM

**Keywords:** FMF, protracted febrile myalgia, auto inflammatory, fever

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## Introduction

Familial Mediterranean fever is a disease described by paroxysmal and self limiting episodes of fever, serositis & synovitis. Sephardic Jews, Armenians, Turkish, and Arabs are predominantly affected through a recessive autosomal mode of transmission.<sup>1</sup>

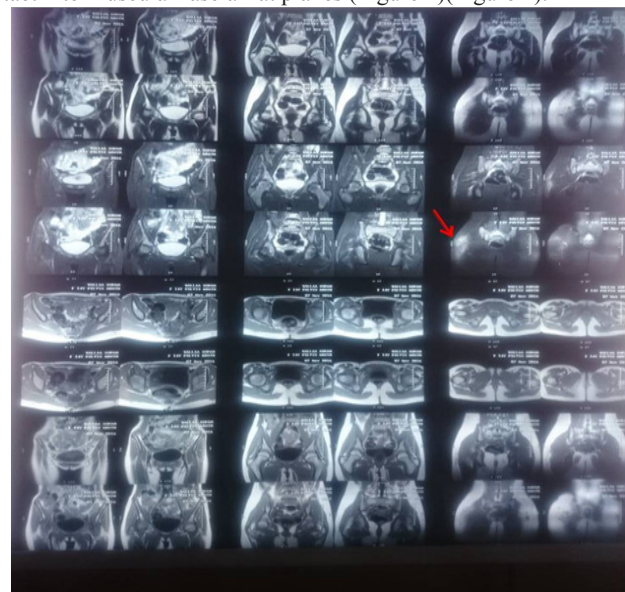
Myalgia is not uncommon musculoskeletal manifestations (occurs in 20%). Protracted febrile myalgia (PFMS), one of muscular pain disorder characterized by severe disabling myalgia, high fever, abdominal pain, diarrhea, arthritis/arthralgia.<sup>2</sup>

High erythrocyte sedimentation rate (ESR), hyperglobulinemia, normal creatinine phosphokinase (CPK), and leukocytosis are the other findings.<sup>3</sup> The episodes last for 4–6 weeks, except in those patients need to be treated with corticosteroids. The PFMS may recur even under colchicine prophylaxis. In this article we describe our case, and also collect & summarize all reported cases from searching on the related references and reviews of literature

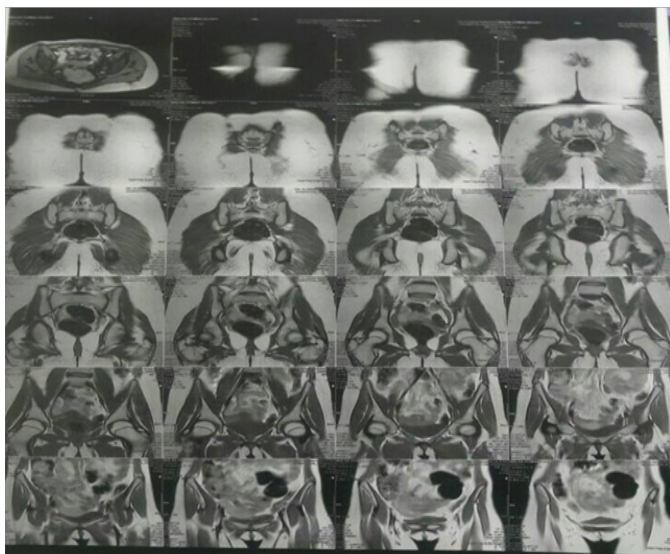
## Case Report

15 yrs old female patient born and lives in Kafr Elsheikh, Egypt was diagnosed to have typical attacks of FMF 5 years ago on colchicine treatment (1.2 mg/d), Molecular genetic study revealed positive heterozygous state, MEFV gene mutations (M694V, E148Q, P369S). The patient has positive family history (her father and uncle have FMF), During the past 6 months, the patient experienced bilateral diffuse, non exertional crippling muscle ach with swelling of both thighs restricting movement of lower limbs, not relieved by colchicine or NSAIDS, the condition was not associated with fever and colicky abdominal pain or skin rash for which she was admitted in the hospital of the faculty of medicine Alex University where initial examination and investigations were done then the patient sought a medical advice in our department. On systematic physical review: The well-developed patient was bedridden in agony normal blood pressure and temperature. Height=145 cms, weight=40 kgs, BMI=19. There was bilateral symmetrical diffuse& tender swelling of both thighs with subcutaneous edema made her unable to move

the lower limbs properly, sensory and motor examination of the upper extremities was normal, Cardiac, chest, abdominal examination was apparently free. Laboratory investigations revealed normal levels of CK, CK-MB, Aldolase & transaminases. Hemoglobin 13.8 g/dL; white blood cell count 5000/mm<sup>3</sup>, platelet count, 209,000/mm<sup>3</sup>; ESR was 14mm/h and high C-reactive protein (CRP) (40 Iu/L). Normal liver & kidney function tests. ASOT within normal range (150 U/ml), ANA, ANCA, RF, serum amyloid A& virology markers for HCV, HBV& CMV were negative Chest X-ray, Abdominal ultrasonography, bilateral lower limb arterial and venous duplex & Ultrasound knee joint showed no abnormalities. MRI of both thigh on presentation showed right posterolateral thigh ill defined patchy area of soft tissue edema involving subcutaneous tissue eliciting high signal in STIR & measured about 10 cm, normal MR musculature appearance with intact intermuscular fascial fat planes (Figure 1)(Figure 2).



**Figure 1** Intermuscular fascial fat planes.



**Figure 2** Electromyogram (EMG) and sensorimotor nerve conduction studies of both lower limbs showed evidence of patchy myopathy.

Electromyogram (EMG) and sensorimotor nerve conduction studies of both lower limbs showed evidence of patchy myopathy. After exclusion the presence of vasculitis which mostly associated with FMF and myalgia induced colchicine; we assumed that the patient had protracted febrile myalgia (PFM), so prednisolone 0.5 mg/Kg was first prescribed but the patient did not improve then we escalate the dose to 1mg/kg/d with extensive physiotherapy for more than 2 months the clinical condition was ameliorated (the Subcutaneous edema & muscle pain subsided & the patient could independently walk) and follow up labs were improved regarding CRP (4 IU/L). Follow up MRI showed no abnormality

Then we started to taper steroids slowly

## Discussion

Familial Mediterranean fever (FMF) is a genetic disease characterized by painful febrile attacks of serositis and systemic manifestations. Since the disease first described in 1945 and the gene of the disease identified in 1992, many sets of criteria were described for the diagnosis. The commonest of these is Tel Hashomer's (Table 1) depending on major and minor criteria.<sup>4</sup> The pathogenesis of FMF<sup>5</sup> is related to exaggerated inflammatory response secondary to abnormal pyrin that has a critical role in the regulation of IL-1 pathway and mutations result in increased IL-1 production, which is believed to be responsible for the clinical characteristics. During episodes, the chemotactic activity of the granulocytes is greatly increased with a massive influx of granulocytes to the affected tissues.<sup>6</sup> Pyrin is expressed only in granulocytes and is likely to be a nuclear factor that controls the inflammatory response in differentiated granulocytes.

The gene responsible for FMF, MEFV, was identified in 1992<sup>7</sup>, and nearly 30 mutations have subsequently been detected.<sup>8</sup> The most common are M694V and V726A. Variable MEFV mutations have different diagnostic, therapeutic, and prognostic implications.<sup>9</sup>

Streptococci might be assumed to be the incriminating agents due to increased ASO titers, circulating immune complexes, hypergammaglobulinemia, and complement component consumption are detected, in patients<sup>10</sup> especially those with vasculitis.<sup>11</sup>

**Table 1** Criteria for FMF diagnosis

Major criteria	Minor criteria
1. Peritonitis,	Incomplete attacks of chest,
2. Pleuritis or pericarditis,	Incomplete attacks of joint (joints other than specified in major criteria)
3. Monoarthritis (hip, knee, ankle),	Exertional leg pain and
4. Fever alone and	Favorable response to colchicine.
5. Incomplete abdominal attacks	

As presented the most important musculoskeletal symptoms is joint involvement, however muscle pain and tenderness may be featured, It has been reported as 20-25% in patients with FMF and has various forms of including myalgia related to Henoch Schönlein purpura and Polyarteritis nodosa, exertional leg pain, fibromyalgia, constitutional generalized myalgia & finally colchicine induced myopathy.<sup>2</sup>

Protracted febrile myalgia (PFM) is a rare pattern (1.2%) of myalgia in FMF. However it may be the first presentation of FMF.<sup>12</sup> It is characterized by episodes of prolonged incapacitating muscle pain & tenderness lasting up to 6 weeks.<sup>3</sup> It is associated by high fever, abdominal pain, diarrhea, arthritis/arthralgia, vasculitic rash, and nephritis. Most of the patients with PFMS bear M694V mutation, However there is a report of PFM case homozygous for E148Q.<sup>13</sup> These attacks are not prevented by colchicine and do not respond to non-steroidal anti-inflammatory drugs. Muscle enzymes are within normal limits with elevated erythrocyte sedimentation rate, hyperglobulinemia & leukocytosis.<sup>14</sup>

MRI can be considered as a valuable tool to diagnose PFMS, the features that suggest PFMS are diffuse edema of subcutaneous fat tissue, increased intensity and contrast enhancement of the muscles and increased signal intensity of vascular beds.<sup>15</sup> Electromyogram (EMG) may be normal or show nonspecific myopathic changes, Muscle biopsy was not feasible in most of diagnosed cases, but of which was done revealed non specific inflammatory infiltration with leucocytes, lymphocytes and eosinophils.

It was peculiar that our young lady case presented with atypical attack of FMF consisting of severe muscle pain & swelling affecting both thigh but not accompanied by fever, rash or abdominal pain. Also ESR was not elevated as expected there is no definite rationale for that; yet the compliance of the patient to colchicine may abort the elevation of ESR as acute phase reactant. We began to revise the history and to put differential diagnosis. Myopathy related to FMF was on the top after exclusion of vasculitis. Hence Fulfilling the clinical criteria, normal CPK levels & characteristic MRI findings (oedema of subcutaneous fat tissue) together with the evidence of inflammatory myopathy by EMG are the hallmarks of diagnosing PFMS and ruling out the colchicine induced myopathy. Immediately, the decision was made based on the foregoing & Steroids were prescribed with collaboration of physiotherapy team for more than 2 months. A good response was achieved and the patient was able to move independently

PFM was first described by Schwabe et al.<sup>16</sup> They noticed the attacks of fever and severe myalgia lasting 10-21 days. In 1988 Schapira et al.<sup>16</sup> described a patient whose only manifestation of FMF was severe myalgia with fever. <sup>17</sup> In 1994 Langevitz et al<sup>17</sup> described 14 FMF patients with severe disabling myalgia accompanied by fever, high erythrocyte sedimentation rate, lasting up to 6 weeks. Transient

vasculitic rashes were reported in few cases.

Kaplan and co decided that there is a strong association between

the M694V mutation and PFM Kaplan et al defined a group of criteria for the diagnosis of PFM in a group of children in 2007.<sup>18</sup>

**Table 2** Adult PFA

Number	Age/ Sex	FMF	Symptoms	Labs	MRI	EMG	Biopsy	FMF gene	Typical FMF	Famiy H/O	Treatment and outcome
1 Bircan Z & Usluer H <sup>28</sup>	15 /M	Known	Abdpain, vomiting, fever and dehydration Myalgia in prox. Ms. 13 yrs ago	Slight Inc ALT, AST Normal CK CRP=12.7 ESR=115 ASOT=303 Virology –ve ANA,P-ANCA-ve				+ve homogenous for M694V mutation	typical	+ve	To colchicine and prednisolone 2mg/kg Follow up : normalization of acute phase reactant
2Bircan Z & Usluer H <sup>28</sup>	12/F	Known	fever, abdominal pain and myalgia	Normal ALT, AST,ALP,CK Normal C3,C4 ESR=113mm/h, CRP26.6 mg/Dl Leucocytosis Serology for hepatitis and lupus –ve ANCA -ve		normal			typical	+ve	prednisolone 2mg/kg Follow up : normalization of acute phase reactant
3 Schapira D et al. <sup>16</sup>	22/F	Not known	Arthritis of ankle, knee joints 16 yrs ago Sever pain in calf mscs with fever	Normal ALT, AST,ALP, CK, aldolase -ve ANA,ASMA, AMA and RF CRP+++ ESR=80		normal	histological:inc in collagen tissue in interstitium with most msc fiber of normal size E/M: most muscle fibres were of normal size with some atrophic cells		Atypical	+ve	No response to prednisolone alone Improved on colchicine 1.5mg/kg Follow up : normalization of acute phase reactant
3 Kotevoglu N et al. <sup>29</sup>	13F	Not known	Sever RT leg and knee ms pain with fever 3 months inability to walk	Normal ALT, AST, ALP Leucocytosis Elevated ESR, CRP and CK	oedema of the subcutaneous fat tissue and the distal part of the medial gastrocnemius muscle prior to the musculo-cutaneous junction of the Achilles tendon	normal	Scarce non specific inflamma-tory infiltrat-ion with leucocyte, lymphocytes and eosinophils	+ve hetregonous for M694V and V726A	Atypical		Respond to steroids and colchicines Follow up : normalization of acute phase reactant
4 ALPAYCI M et al. <sup>21</sup>	33 M	Not known	Sever paralyzing myalgia, abd pain, fever, muscle tendrness	Normal ALT, AST, CK, ASOT, RF -ve virology Leukocytosis ESR=36 CRP=51				+ve heterozygous V726A	typical		Respond to steroids and colchicines Follow up : normalization of acute phase reactant

Table Continued.....

Number	Age/ Sex	FMF	Symptoms	Labs	MRI	EMG	Biopsy	FMF gene	Typical FMF	Famiy H/O	Treatment and outcome
5 Tufan G & Demir S <sup>23</sup>	30F	known	Sever diffuse ms pain and tenderness For 2 months	Normal CK, ALT, AST leucocytosis -ve ANA, antiDNA, ANCA ESR = 140 CRP=158							No response to colchicine alone Respond to added steroids , tapered then stopped Follow up : normalization of acute phase reactant
6 Fujikawa Ket al. <sup>130</sup>	22M	known	Fever, prolonged myalgia of both UL and LL, abd pain , diarrhea For 3 weeks	Normal CK Aldolase=6.6 high ESR & CRP ferritin=566 -ve virology	Thickening of fascia in STIR suggestive of Fasciitis		striking changes appear in the fascia, including an increased amount of collagen fibrils and infiltration by fibroblasts, macrophages and a few mast cells	+ve homozygous for E148Q and compound heterogenous P3695-R408Q	typical	+ve	Respond rapidly to small dose steroid 20mg/d and discontinued along 6 weeks Follow up : normalization of acute phase reactant
7 Ertekin et al. <sup>31</sup>	14 M	known	Fever,abd pain, sever myalgia all mscs For 25 days	Normal ALT,AST,CK -ve ANA ESR=92mm/h CRP=15mg/dl				+ve heterozygous mutation E148Q and R761	typical	+ve	Respond to steroids within 10 days Follow up : normalization of acute phase reactant
8 Ridvan M et al. <sup>32</sup>	41F	Known 2yrs ago	severe calf and thigh pain, fever and malaise 4 weeks duration	Normal ALT,AST,CK Leucocytosis ESR=84 CRP=178	MRI revealed remarkable muscle oedema in her calf muscles			heterozygous M694V mutation	typical		Steroid +colchicine recurrence anaqkinra 100mg /day s.c response Follow up : normalization of acute phase reactant
9 Ridvan M et al. <sup>32</sup>	44F	Known 27yrs ago	severe right thigh pain for 3 weeks. She also complained of diarrhoea and ankle pain	Normal ALT,AST,CK ESR=78 CRP=66				homozygous for M694V mutation	typical		Naproxen +colchicine no response Anakinra 100mg /day s.c response Follow up: normalization of acute phase reactant
10 Senel K et al. <sup>33</sup>	12/M	Known to be FMF	LL pain , skin rash,fever inability to walk	Normal muscle enzymes CRP=12 ESR=108 ASOT=601 Leukocytosis Virology -ve		Non-specific changes		homozygous for M694V mutation			Steroides for 3 weeks Follow up: normalization of acute phase reactant

Table Continued.....

Number	Age/ Sex	FMF	Sym ptoms	Labs	MRI	EMG	Biopsy	FMF gene	Typical FMF	Famiy H/O	Treatment and outcome
11 Soylu et al. <sup>13</sup>	14/F	Not known to have FMF	UL & LL myalgia, fever & arthralgia	Normal muscle enzymes CRP=183 ESR=102 ASOT =Normal Leukocytosis Virology -ve ANA,Anti-dsDNA, P-ANCA, C-ANCA -ve				homozygous E148Q	atypical		Improved after 24 hrs from intake of steroids prednisolone 2mg/kg/day Follow up : normalization of acute phase reactant
12 Brican Z <sup>22</sup>	12/F	Known	Abd pain fever Vomiting diarrhea Sever myalgia Skin rash convulsion	Normal muscle enzymes leucocytosis ESR=115 CRP13.3 ASOT: normal ANA,ANCA -ve Virology -ve		Normal		homozygous for the M694V	typical		prednisolone 2mg/kg or more than 62 days Follow up: normalization of acute phase reactant
The patient of this report	15/F	Known	Severe bilateral thigh pain and swelling not associated with fever or abdominal pain for 2 weeks	Normal muscle enzymes ESR=15 CRP: 47 ASOT: normal Virology & ANA negative	subcutaneous tissue dema with intact musculature		patchy myopathy	Heterozygous for (M694V , E148Q , P369S)	typical	+ve	Steroids 1mg/kg/d for 10 weeks began to improve after 1 month of treatment

I. Obligatory criteria:

- a. FMF-Prior clinical and/or genetic evidence of FMF or familial history of FMF.
- b. 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.
- c. Duration of symptoms-Persistence of the myalgia for ≥5 days.

II. Supporting criteria:

- a. Homozygosity/hemizygosity for M694V mutation.
- b. Elevated levels of inflammation markers: ESR≥80mm/h, CRP≥5mg%.
- c. Fever≥38.0°C.

III. Exclusion criteria:

- a. Polyarteritis nodosa(PAN)

PFMS is thought to be a vasculitic process although the supporting pathologic evidence is lacking.<sup>19</sup> Interestingly, other vasculitides such as Henoch Schonlein, Bechet’s disease, and poly-arteritis nodosa have been found in an increased incidence among FMF patients.<sup>20</sup> The exact mechanism describing the pathophysiology of PFMS is unknown, but

there may be triggering factors such as an infection, or an interaction with other proteins induced by stress, trauma or hyperthermal balneotherapy,<sup>21</sup> these factors regulate the immune response evolving in to an inflammatory state of PFMS in some FMF patients.<sup>22</sup>

Although colchicine is the cornerstone of FMF treatment, it has clearly been non effectious for PFMS. Corticosteroids is the mainstay in treatment. Though with high-dose steroids elicits resolution of symptoms in 5 –7days,<sup>18</sup> It may need prolonged time of intake more than 6weeks for good response.<sup>23</sup> Moreover, corticosteroids may not be beneficial in some patients , thus the use of other immunosuppressive was issued in various cases.<sup>24</sup> To date, immunomodulatory agents like interferon, and tumor necrosis factor inhibitors have been employed in refractory & severe cases of FMF with variable success but not issued in PFM perse.<sup>25</sup>

Demonstration of pivotal role of interleukin-1 (IL-1) in the pathogenesis of FMF leads to the use of IL-1 blockers in colchicine resistant or intolerant patients, Interleukin-1 (IL-1) antagonists, as anakinra, canakinumab and rilon accept are reported to be effective in colchicine unresponsive FMF patients.<sup>26-27</sup>

After reviewing the literatures; all reported cases of adolescence and adult PFM and our case are summarized in Table 2. <sup>[13,18,21-23,28-33]</sup> Up to that time we found 13 cases of FMF developed PFM. Their age range 12-44yrs with mean age 28±16. Five cases of them were males (38.46%) & 8 (61.53%) females. Five of them with documented positive family history (38.46%) and one patient (7.69%) with

reported negative family history. Nine (69.23%) patients were known to have FMF before the emerging the PFM while the rest of patients (30.7%) diagnosed to have FMF at the onset of presentation. All patients shared the typical muscle ach and tenderness, only 8 of them; fever was associated. Normal muscle enzymes with high ESR & CRP were the remarkable lab in diagnosis of all PFM cases. Three of the cases (23.07%) were positive hetregonous for M694V and V726A; three (23.07%) were positive homozygos for M694V while one patient (7.69%) harboured homogenous for E148Q and compound heterogenous P3695-R408Q; while two case(14.38%) beard positive heterozygous mutation E148 and R764.

Out of the cases, three (23.07%) only underwent musckuloskeletal MRI on the affected muscles which revealed subcutaneous and muscle oedema, EMG was done in four cases(30.7%) [normal EMG findings done in 3 (23.07%) cases only, non specific changes in one patient (7.69%). Muscle biopsy was taken in 2 patients which demonstrated histological examination of the striated muscle did not show signs of vasculitis. There was an increase of the collagen tissue in the interstitium of the muscle and also a few inflammatory cells. The electron microscopic examination showed most muscle fibres were of normal size, but atrophic muscle cells of 17-20 im were dispersed. The sarcomere pattern was well preserved. The perivascular basement membrane of capillaries and of small venules was uniformly and moderately widened and the interstitium was infiltrated with fibroblasts, macrophages, and a few mast cells.<sup>16</sup>

Mostly of the patients [10(76.9%)] responded well to steroids while 2 cases showed steroid resistance and achieved proper improvement on the use of an IL-1 inhibitor, anakinra. Owing to the scarcity of studies about the management of steroid resistant PFM, we hereby declare the urgent need to evaluate the management of PFM & variable response to different medication which might be related to phenotypic characteristics such as age of onset, ethnicity, Clinical presentation as well as frequency & the severity of the attacks aside of the genotypic features. Herein, we reported a successful treatment with prolonged use of high dose steroids along 10 weeks with extensive physiotherapy

## Conclusion

FMF can be considered to be recognized easily with the classical features including abdominal pain, fever, pleuritis, arthralgia & myalgia. The atypical presentation of PFMS with severe disabling muscle pain and prolonged weakness may be a rare pattern of FMF. We would like to point out that FMF with PFM which respond well to steroids & immunosuppressive drugs to reduce the time of pain and complications.

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None.

## Conflict of interests

The author declares there is no conflict of interest.

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