

# Corticosteroid-resistant anakinra-responsive protracted febrile myalgia syndrome as the first manifestation of familial Mediterranean fever

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## ABSTRACT

Familial Mediterranean fever (FMF) is the most common type of monogenic periodic fever syndromes and characterized by recurrent self-limited attacks of fever and polyserositis. Musculoskeletal signs and symptoms are not uncommon and manifested as arthritis and myalgia. Myalgia may be spontaneous or exercise induced that mostly affects lower limbs and spontaneously resolves in 2–3 days. Protracted febrile myalgia syndrome (PFMS) is another form of rare and severe muscle involvement in FMF. It affects all muscle groups and lasts for several weeks. Herein we present a pediatric case of PFMS that presented as the first manifestation of FMF, not responded to prednisolone at all, but showed dramatic improvement with anakinra. Our case has a few distinctive points. She did not have diagnosis of FMF and also she did not have any previous complaints compatible with FMF. So, PFMS was the first sign of FMF in this patient. Most of the cases of PFMS show dramatic response to corticosteroids but our case did not respond at all to high-dose corticosteroids and anakinra resulted in rapid resolution of the symptoms. Protracted febrile myalgia syndrome may be the first manifestation of FMF. It should be suspected in cases with prolonged and unexplained fever, severe myalgia, and high acute phase reactants.

*Keywords:* Anakinra; familial Mediterranean fever; protracted febrile myalgia syndrome.

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Familial Mediterranean fever (FMF) is an autoinflammatory disorder caused by mutations in the MEFV gene and characterized by recurrent attacks of fever, abdominal pain, chest pain, and arthritis [1].

Muscle involvement in FMF is reflected as myalgia and may be in the form of spontaneous or exercise induced myalgia lasting less than 2–3 days that usually affects lower limbs. The other form, protracted febrile myalgia syndrome (PFMS), is a very rare but severe manifestation of FMF that is characterized by severe debilitating pain in large muscle groups with accompanying fever that may last for several weeks. Most of the PFMS patients show dramatic improvement with corticosteroid treatment [1, 2].

## CASE REPORT

A 5-year-old girl was referred to our clinic with fever, abdominal pain and severe myalgia in the upper and lower limbs for two weeks and inability to walk for the last few days. She had neither history of recurrent fever, peritonitis, pleuritis, arthritis, nor family history of FMF. In physical examination, the fever was 38.7°C, and she had diffuse sensitivity and tenderness in the abdomen, upper and lower extremity muscle groups without any rash, organomegaly or lymphadenopathy. Arterial blood pressure and neurological examination was normal with normal deep tendon reflexes and intact sphincter functions. She was bedridden and refusing to walk because of diffuse myalgia.

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Laboratory tests showed leukocytosis (leukocytes: 18.400/mm<sup>3</sup> with 89% neutrophils), thrombocytosis (platelets: 539.000/mm<sup>3</sup>), and high acute phase reactants; C-reactive protein (CRP): 226.5 mg/L (normal <6 mg/L), erythrocyte sedimentation rate (ESR): 75 mm/h, and serum amyloid A: 550 mg/L (normal <6.8 mg/L). Other laboratory tests including liver and kidney function tests, muscle enzymes, electrolytes, anti-streptolysin O (ASO) titers and urinalysis were within normal limits.

We have excluded possible metabolic, infectious and malignant etiologies by biochemistry, culture, serology and bone marrow aspiration studies. Colchicine 0.5 mg/day and intravenous high-dose methylprednisolone (30 mg/kg/day, 3 days) followed by 2 mg/kg/day prednisolone were started with the working diagnosis of PFMS. Despite two weeks of corticosteroid treatment diffuse and severe myalgia and high acute phase reactants persisted. On the 2<sup>nd</sup> week of corticosteroid treatment, anakinra (2 mg/kg/day, sc) was started. Severe myalgia resolved dramatically a few hours after the first dose of anakinra and acute phase reactants became normal within a few days. Prednisolone treatment was discontinued on the 1<sup>st</sup> week of anakinra and anakinra was used for a month.

Genetic analysis showed homozygous M694V mutation in the MEFV gene. She is being followed for two years and she had one attack of right ankle arthritis and erysipelas-like erythema without fever under colchicine treatment during this period. Written informed consent was received from the family.

## DISCUSSION

Hereditary periodic fever syndromes are a group of monogenic disorders manifesting with recurrent fever and inflammation [1]. The term autoinflammation was used first time in 1999 to describe a family of clinical disorders characterized by recurrent episodes of inflammation without high-titer autoantibodies or antigen-specific T lymphocytes [3]. Monogenic autoinflammatory diseases are primarily inborn errors of innate immunity contrary to the autoimmune diseases that are secondary to errors of the adaptive immunity [1, 3].

Familial Mediterranean fever is the prototype of the periodic fever syndromes and is caused by mutations in the Mediterranean fever (MEFV) gene [1]. MEFV gene encodes the protein pyrin. Gain of function mutations in

the gene lead to activation of pyrin inflammasome and overproduction of interleukin-1, causing to inflammation [4]. FMF is most commonly seen in the countries of Mediterranean basin and highest prevalence is observed in Turks, Armenians, Sephardic Jews and Arabs [1]. The disease is characterized by recurrent self-limited attacks of fever and serositis. Typical attacks last 12 to 72 hours and recur every 1 to 2 months with fever, peritonitis, pleuritis, arthritis and erysipelas like erythema. It is known that patients with homozygous exon 10 mutations, particularly M694V mutations, tend to have a more severe and complicated course [1, 5].

Muscle involvement in FMF is reflected as myalgia and may be spontaneous or exercise induced that last less than 2–3 days and spontaneously resolves. One of the most severe and rare manifestations of FMF is PFMS that is characterized by severe, long lasting, debilitating myalgia [6, 7].

Protracted febrile myalgia syndrome was first described by Langevitz et al. in 1994 [8]. Kaplan et al. proposed diagnostic criteria set that includes obligatory criteria as having diagnosis of FMF, upper and/or lower limb myalgia with normal muscle enzymes, and the persistence of myalgia  $\geq 5$  days and supportive criteria as having at least one M694V mutation, elevated ESR and CRP and fever  $\geq 38^{\circ}\text{C}$  [9]. Our case neither had diagnosis nor had any previous symptom or sign compatible with FMF, and PFMS was the first symptom of FMF.

The etiopathogenesis of PFMS in FMF is poorly understood. It is well known that children with FMF are more prone to vasculitis such as Henoch-Schönlein purpura and poliarteritis nodosa (PAN) [10]. PFMS is also considered as a form of vasculitis due to presence of skin rash in some cases but histopathological evidence supporting this opinion is lacking [10, 11]. Bircan et al. reported 6 cases of PFMS and in 4 of them provisional diagnosis was PAN. The rapid resolution of symptoms with corticosteroids and normal angiography made them exclusion of PAN [12]. There are also some reports about streptococcal infections being as triggers of PFMS [2, 13]. Duru et al. presented two cases of PFMS with elevated ASO titers and they concluded that streptococcal infections may be environmental triggers of PFMS [2]. We did not suspect PAN in our case as she did not have any rash or hypertension. The child had normal ASO titers and family was denying any recent infection, so we were unable to demonstrate any possible environmental trigger for PFMS.

Colchicine is the mainstay treatment in FMF but does not prevent development of PFMS. Corticosteroids show dramatic improvement in the symptoms of PFMS. But there are corticosteroid resistant cases in the literature [14]. The elucidation of pathogenesis of FMF has led to the use of interleukin-1 blockers in colchicine resistant FMF patients and also in corticosteroid-resistant PFMS patients [1, 5, 14]. Mercan et al. presented two adult FMF patients with corticosteroid-resistant PFMS. Both cases showed dramatic improvement the day after the first anakinra injection [14]. Our case did not show any response to high doses of corticosteroids but severe myalgia resolved just in a few hours of the first anakinra dose.

In conclusion, protracted febrile myalgia syndrome may be the first manifestation of FMF. It should be suspected in cases with prolonged and unexplained fever, severe myalgia, and high acute phase reactants. Anakinra seems to be an alternative in corticosteroid-resistant cases with fast and complete resolution of PFMS symptoms.

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