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CASES WITH A MESSAGE

Protracted febrile myalgia as a challenging manifestation of familial Mediterranean fever: case-based review

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Abstract

Protracted febrile myalgia syndrome (PFMS) in familial Mediterranean fever (FMF) patients is a vasculitic condition characterized by severe myalgia, fever, abdominal pain, diarrhea, and arthralgia/arthritis episodes lasting 4–6 weeks. Symptoms typically resolve with corticosteroid treatment. However, in recent years, corticosteroid-resistant PFMS patients have been reported. We herein report five pediatric FMF patients complicated with PFMS. In addition, demographic findings, Mediterranean fever (*MEFV)* gene analysis, symptoms at disease onset, time interval between the diagnoses of FMF and PFMS, co-existent diseases, and treatment responses were evaluated. Resolution of all PFMS symptoms was accepted as complete response, while decreased symptoms without full recovery as partial response. We searched PubMed using the keywords 'protracted febrile myalgia' and 'anakinra', and reviewed the literature. There were three male and two female patients. Median age at the diagnosis of FMF was 6 (3–10) years. The time from diagnosis of FMF to the development of PFMS was changed from 0 to 8 (median: 2) years. All of the patients, except one, had homozygous *M694V* mutation. All patients were treated with corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) first. Two out of five patients were exhibited partial response, while others exhibited complete response. Patients with partial response to the conventional therapies were treated with anakinra, and achieved a great response after the first dose. Anti-interleukin-1 (IL-1) therapy may be a beneficial and a reasonable treatment option, when there is insufficient response to NSAID and corticosteroid therapies in pediatric PFMS patients.

Keywords Familial Mediterranean fever · Protracted febrile myalgia syndrome · Anakinra · Corticosteroids

Introduction

Familial Mediterranean Fever (FMF) is an autosomal recessive inherited autoinflammatory disorder characterized by self-limited sterile serositis attacks [1]. The *Mediterranean fever* (*MEFV*) gene on chromosome 16p encodes the protein pyrin, the mutation of which causes inflammasome hyperactivation, resulting in typical FMF attacks [2]. Various *MEFV* mutations have been identified, such as *M694V, M680I, V726A*, and *P369S*. The *M694V* homozygous mutation is responsible for the most severe phenotype including amyloidosis, vasculitis, protracted arthritis, and myalgia [3]. Colchicine treatment remains the mainstay to prevent inflammatory attacks and the development of amyloidosis [4]. In recent years, anti-interleukin-1 (IL-1) therapies have been successfully used to suppress inflammation in colchicine-resistant patients [5].

Protracted febrile myalgia syndrome (PFMS) in FMF patients was first described by Langevitz et al. as a vasculitic condition characterized by severe myalgia, fever, abdominal pain, diarrhea, and arthralgia/arthritis episodes lasting for 4–6 weeks [6]. A vasculitic rash mimicking immunoglobulin A (IgA) vasculitis may also be seen. The initial presentation of protracted fever and myalgia can make the diagnosis of FMF challenging. Laboratory work-up exhibits normal creatinine phosphokinase (CPK) and high inflammatory markers, including C-reactive protein (CRP), erythrocyte

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sedimentation rate (ESR), and fibrinogen [6, 7]. Group A *streptococcus* infections may trigger PFMS episodes [8, 9]. PFMS can also develop in patients already receiving colchicine therapy, and symptoms typically resolve with corticosteroid treatment [8]. However, corticosteroid-resistant PFMS patients have also been reported [10]. Recently, Mercan et al. reported two adult PFMS patients who were successfully treated with anti-IL-1 therapy administered for only 2 days [11].

In this study, we report our experience with five pediatric PFMS cases, including clinical findings, laboratory data, and treatment response. We emphasize the beneficial role of anti-IL-1 therapy in two cases that exhibited an insufficient response to corticosteroid and non-steroidal anti-inflammatory drug (NSAID) therapies. This is the first report on anti-IL-1 therapy in pediatric PFMS patients who had insufficient responses to classic therapies.

Methods

We collected data on five pediatric FMF patients with PFMS complications, who were followed at our clinic from 2015 to 2018. Each patients' age, gender, *MEFV* gene analysis, acute-phase reactants, age at diagnosis, symptoms at disease onset, duration between the diagnoses of FMF and PFMS, co-existing diseases, and treatment responses were noted. Clinical responses were evaluated according to the response of therapies: resolution of all PFMS symptoms was accepted as a complete response, while decreased symptoms without full recovery as a partial response. Informed consent was obtained from the patients and their parents. We searched PubMed using the keyword 'protracted febrile myalgia' and 'anakinra', and reviewed the current literature (Fig. 1). We investigated gender, age at PFMS diagnosis, time from FMF diagnosis to PFMS, *MEFV* mutation analysis, treatment strategies, and clinical findings. We searched the English literature from inception to November 2017. Editorial letters and abstracts were excluded.

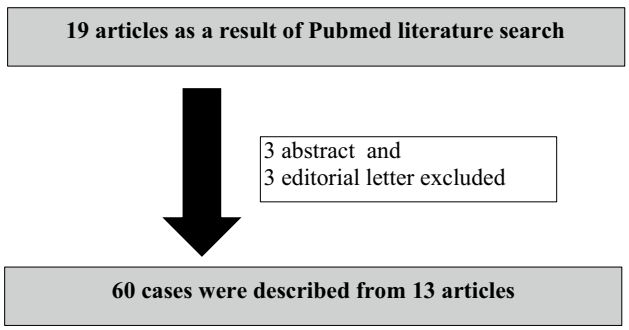

Fig. 1 Pediatric febrile myalgia syndrome (PFMS) studies included in the literature research

Results

The five patients' clinical, demographic, and genetic findings are shown in Table 1. All but one of the FMF patients fulfilled the proposed criteria for PFMS [12], including severe disabling myalgia of at least 5-day duration associated with fever, elevated inflammatory markers and the presence of at least one *M694V* mutation. While four out of five patients had the *M694V* homozygous mutation, one had *M680I* homozygous with an aggressive phenotype. All infectious, malignant, or other vasculitic diseases were excluded. Patient 5 had purpura on the lower extremities, mimicking IgA vasculitis and polyarteritis nodosa (PAN). However, there were no other clinical signs for these two conditions in case 5, such as hypertension, livedo reticularis, peripheral neuropathy, renal involvement, gastrointestinal bleeding, or arterial abnormalities. The male:female ratio was 3:2. None of the patients had amyloidosis or proteinuria, and all were of Turkish origin (Central and Northern Turkey). FMF was diagnosed at the age of 3–10 (median 6) years. The median time from FMF diagnosis to PFMS was 2 (0–8) years. Only patient 2 presented to our clinic with fever, abdominal pain, and paralyzing myalgia, and she was diagnosed with PFMS associated with FMF. This patient exhibited four recurrent PFMS episodes during the 3-year follow-up period. The other four patients had been diagnosed with FMF before presenting with severe myalgia. All patients had markedly elevated inflammatory markers, but none had elevated CPK levels. Anti-streptolysin O (ASO) levels were remarkably high in three patients. All patients were administered 15-mg/kg naproxen daily and 2-mg/kg prednisolone daily was given to patients with an insufficient response. Patients 2 and 5 partially responded to corticosteroid therapy, while the others completely responded. Anakinra 2-mg/kg daily was prescribed to these two patients, and their symptoms immediately resolved on the first day. The elevated inflammatory markers were decreased with these anti-inflammatory therapies. Corticosteroid therapy was tapered gradually and ceased within a month, and anti-IL-1 therapy was continued for 3 months. There were no treatment-related adverse effects either with anti-IL-1 or with corticosteroids or NSAIDs (Table 1).

Discussion

The present study describes the clinical, genetic and demographic characteristics of five pediatric FMF patients complicated with PFMS and contains a literature review (Table 2). In cases defined in the literature, age at PFMS

Table 1 Clinical, demographic, genetical characteristics, laboratory parameters, and treatment responses of five patients with protracted febrile myalgia syndrome

Pt no.	Sex	Region of Turkey	Age in years	Age of dx (years)	Time from dx to onset PFMS (years)	Time since PFMS symptom onset (days)	*MEFV* gene mutation	ASO(IU/ml) NR:0-150	ESR (mm/h) NR:0–20/CRP (mg/dl) NR:0–5			Clinical findings	Prednisolon dose (mg/kg)	Response to prednisolon	Response to anti-IL-1 agent
									First visit	Post corticosteroid[a]	Post-anti-IL-1[a]				
1	Male	Central Anatolia	10	4	5	21	*M694V/M694V*	3150	93/57	76/33	–	Fever, abdominal pain, severe myalgia	2	Complete response	–
2	Female	North Anatolia	11	6	0	14	*M694V/M694V*	3370	84/99	46/23	8/3	Fever, recurrent severe myalgia (4 times)	2	Partial response	Complete response
3	Male	North Anatolia	13	10	2	10	*M680I/M680I*	N/A	74/141	37/18	–	Fever, severe myalgia	1	Complete response	–
4	Male	Central Anatolia	10	9	1	21	*M694V/M694V*	2160	83/105	51/47	22/11	Fever, abdominal pain, severe myalgia	2	Partial response	Complete response
5	Female	North Anatolia	11	3	8	7	*M694V/M694V*	N/A	51/49	24/39	–	Fever, abdominal pain, severe myalgia, purpura	2	Partial response	–

Pt patient, *PFMS* protracted febrile myalgia syndrome, *MEFV* Mediterranean fever, *ASO* anti-streptolysin O, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *NR* normal range, *IL-1* interleukin-1, *dx* diagnosis, *NA* not available

[a]At the end of first week of therapy

Table 2 Reported series and case reports of protracted febrile myalgia syndrome

Study	Female/male	Age in years, (min–max values)	Number of FMF patients with PFMS	Time from dx to onset PFMS years, (min–max values)	MEFV gene mutation	Treatment	Clinical findings
Langevitz et al. [6]	10/4	3–45	14	2–32	*M694V*	Corticosteroid	Severe myalgia, fever, abdominal pain, arthralgia/arthritis, diarrhea, skin eruption
Ertekin et al. [14]	1/1	11–14	2	0	*M694V/M694V, E148Q/R761H*	Corticosteroid	Severe myalgia, fever, abdominal pain
Soylu et al. [8]	2/4	5–12	6	0	*M694V/M694V (3), M694V/M680I (2), M694V/V726A (1)*	Corticosteroid	Severe myalgia, fever, abdominal pain, arthralgia/arthritis, skin eruption
Kaplan et al. [12]	NA	NA	15	5–12	*M694V (14)*	Corticosteroid (4), NSAID (9)	Severe myalgia, fever
Bircan et al. [15]	0/6	6–12	6	0	*M694V/M694V (2)*	Corticosteroid	Severe myalgia, fever, abdominal pain, arthralgia/arthritis, hypertension
Tufan et al. [16]	1/0	30	1	10	*NA*	Corticosteroid	Severe myalgia
Duru et al. [17]	0/2	8	2	0–1	*M694V/-(1), M694V/M694V (1)*	Corticosteroid	Severe myalgia, fever, abdominal pain, arthralgia/arthritis, purpura
Senel et al. [18]	0/1	12	1	0–10	*M694V/M694V (1)*	Corticosteroid	Severe myalgia, fever, purpura
Demir et al. [19]	0/1	11	1	0	*M694V/M694I (1)*	Corticosteroid	Severe myalgia, abdominal pain, with newly diagnosed type I diabetes mellitus
Fujikawa et al. [7]	0/1	22	1	0	*E148Q/P369S/R408Q (1)*	Corticosteroid	Severe myalgia, abdominal pain, diarrhea, headache
Abdel Halim et al. [20]	0/1	34	1	15	*M694V/M694V (1)*	Corticosteroid	Severe myalgia, fever, abdominal pain, diarrhea, pupura, pleuritic chest pain, after the kidney transplantation
Mercan et al. [11]	2/0	41–44	2	2–27	*M694V/- (1), M694V/M694V (1)*	*Anakinra*	Severe myalgia, fever, abdominal pain, arthralgia, diarrhea, hypertension
Rom et al. [13]	6/2	6–17	8	0–14	*M694V/M694V (6), M694V/E148Q (1), M694V/V726A (1)*	*Pulse corticosteroid*	Severe myalgia, abdominal and chest pain
Gezgin Yildirim et al. (present study)	2/3	3–10	5	0–8	*M694V/M694V (4), M680I/M680I (1)*	*NSAID, Corticosteroid, Anakinra*	Severe myalgia, fever, purpura, abdominal pain

FMF familial Mediterranean fever, *PFMS* protracted febrile myalgia syndrome, *NSAID* non-steroidal anti-inflammatory drugs, *MEFV* Mediterranean fever, *min* minimum, *max* maximum, *dx* diagnosis, *NA* not available

*Corticosteroid treatment was administered oral as prednisolone 1–2 mg/kg per day for 1–2 months. Pulse corticosteroid treatment was administered intravenous as 10 mg/kg per day for 3 day consecutively, and then 1–2 mg/kg per day oral prednisolone for 6 weeks

attack was changing between 3 and 44 years. In addition to *M694V* homozygous mutation, there were PFMS cases with other *MEFV* mutations, such as *V726A, P369S, R761H*, and *M680I*. In line with this, our case 3 had homozygous *M680I* mutation. The PFMS is mainly treated with corticosteroids, and in the mild cases, even NSAIDs are adequate [6–8, 11–20]. There is a lack of information in the literature on treatment options for corticosteroid-resistant PFMS. In the present series, the symptoms in two corticosteroid-resistant PFMS patients were controlled with anakinra. In the remaining three patients, the clinical response to corticosteroid treatment was excellent. There is no guideline regarding the duration of anti-IL-1 therapy in PFMS patients. Anakinra was administered for 3 months to suppress inflammation and to prevent PFMS attacks in FMF patients with an aggressive phenotype in childhood. In particular, patient 2 had exhibited four PFMS episodes over 3 years.

Our literature review found 60 cases (pediatric and adult) reported in 13 articles, the majority of whom were treated with corticosteroids and NSAIDs. The clinicians mainly preferred prednisolone at a dose of 1–2 mg/kg/day. Rom et al. evaluated the effect of pulse methylprednisolone (10 mg/kg) therapy over 3 days in eight pediatric PFMS patients using a visual analog scale (VAS), and reported a prompt clinical response [13]. Recently, Mercan et al. reported two adult PFMS patients successfully treated with anakinra (100 mg/day) for only 2 days. Corticosteroid treatment was not administered before anti-IL-1 therapy due to co-existing essential hypertension [11]. Despite satisfactory clinical response to anti-IL 1 therapy in adult PFMS patients [11], there are no existing data on the use of anti-IL-1 in pediatric PFMS patients who are unresponsive to the conventional treatment. In this context, we herein reported the beneficial effect of anti-IL-1 therapy in pediatric PFMS for the first time.

Conclusion

PFMS, a rare vasculitic manifestation of FMF, may be a diagnostic challenge in previously undiagnosed FMF patients. Corticosteroids remain the main treatment, not only to alleviate clinical symptoms but also to suppress inflammation. Anti-IL-1 therapy may be suggested as a beneficial treatment option for PFMS patients with insufficient response to NSAID and corticosteroid therapies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest for any pharmaceutical companies.

Informed consent Written informed consent was obtained from the patients and their parents for publication of this article.

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