Ocular inflammatory diseases in children with familial Mediterranean fever: a true association or a coincidence?

Pinar Ozge Avar-Aydin (pinarozgeavar@gmail.com)
Ankara University Faculty of Medicine: Ankara Universitesi Tip Fakultesi https://orcid.org/0000-0002-7469-109X
Nilgun CAKAR
Ankara University Faculty of Medicine: Ankara Universitesi Tip Fakultesi
Zeynep Birsin OZCAKAR
Ankara University Faculty of Medicine: Ankara Universitesi Tip Fakultesi
Nilufer YALCINDAG
Ankara University Faculty of Medicine: Ankara Universitesi Tip Fakultesi
Fatos YALCINKAYA
Ankara University Faculty of Medicine: Ankara Universitesi Tip Fakultesi

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Abstract

Purpose: To describe the characteristics of patients with familial Mediterranean fever (FMF) concurrent with ocular inflammatory disease (OID) and to criticize possible relations between them.

Methods: Clinical data were extracted from electronic medical records. Additionally, the medical literature on OIDs in FMF was reviewed.

Results: Among 512 pediatric patients with FMF, five patients were found to have OIDs: bilateral chronic uveitis, recurrent orbital myositis (ROM), recurrent optic neuritis, and acquired Brown's syndrome. The first cases of ROM and acquired Brown's syndrome in FMF have been introduced in the literature. All patients presented with early-onset typical FMF attacks carried at least one M694V mutation and experienced OID while on colchicine.

Conclusion: Increased frequency of OIDs in FMF as per the pediatric population and relapsing and chronic course of OIDs occasionally with concurrent FMF attacks suggest that this inflammatory syndrome especially those carrying M694V mutations may be a predisposing factor for OIDs.

Introduction

Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease caused by excessive activation of the pyrin inflammasome derived from the MEFV (MEditerranean FeVer) gene mutations on chromosome 16p [1]. Typical clinical presentation is recurrent spontaneously resolving episodes of fever and polyserositis (peritonitis, pleuritis, pericarditis, synovitis) that last between 1–3 days accompanied by an increase in serum acute phase reactants (sAPR) [2]. Colchicine is the main treatment regimen that prevents febrile episodes and secondary amyloidosis [3]. Because of increased IL-1β activation during FMF episodes, IL-1 inhibitor drugs have been increasingly used in the case of colchicine resistance or intolerance [4].

The association of FMF with other inflammatory diseases such as spondyloarthritis, immunoglobulin A vasculitis/Henoch-Schönlein purpura, polyarteritis nodosa, inflammatory bowel disease (IBD), chronic arthritis, and protracted febrile myalgia has been well defined and it is suggested that FMF and associated inflammatory diseases should not be considered as the coexistence of different clinical entities [5–8]. Previous studies have reported uveitis, scleritis, episcleritis, optic neuritis, and frosted branch angiitis of retinal vein among ocular inflammatory manifestations of FMF [9–14]. Although FMF has been thought of as a predisposition to a variety of inflammatory processes, the possible association of FMF with ocular inflammatory diseases (OIDs) is not clear contrary to its known association with sacroiliitis, vasculitis, and IBD.

Herein, we aimed to describe the characteristics of OIDs observed in children with FMF and to criticize possible relations between these two inflammatory entities. Further, the medical literature on OIDs in FMF was reviewed.

Material And Methods

Demographic and clinical data were extracted from the electronic medical records of patients with FMF and concurrent OIDs followed in the Department of Pediatric Rheumatology of Ankara University School of Medicine in the last 5 years. The diagnosis of FMF was based on Yalcinkaya criteria [15]. Ocular inflammatory diseases were diagnosed and treated in collaboration with the Department of Ophthalmology.

Demographic features, family history, clinic and laboratory findings, genetic analysis of MEFV gene mutations, and laboratory tests done for the differential diagnosis of the particular OID were recorded. Routine ophthalmic examination

included the assessment of visual acuity, intraocular pressure, slit lamp, and dilated fundus examinations. Standardization of Uveitis Nomenclature criteria was used to classify uveitis [16]. At least six mutations in the MEFV gene including p.M694V, p.M694I, p.M680I, p.V726A, p.K695R, and p.E148Q were analyzed. Exon 10 mutations were screened by direct sequencing of the polymerase chain reaction (PCR)-amplified fragments and p.E148Q mutation in exon 2 by PCR-restriction fragment length polymorphism protocol. Serum biochemistry, urinalysis, an infectious screen, autoantibodies, HLA testing, serum angiotensin-converting enzyme level, and a chest X-ray were carried out to investigate the etiology of OID. Infectious tests were performed for the identification of tuberculosis, toxoplasmosis, syphilis, Lyme disease, cytomegalovirus, herpes simplex virus, rubella, leptospirosis, and varicella-zoster virus. Cranial imaging was performed except for patients with uveitis.

The Pubmed database was searched using the following keywords: “familial Mediterranean fever” AND “ocular inflammatory disease” OR “ocular involvement” OR “eye involvement” OR “uveitis” OR “scleritis” OR “optic neuritis” OR “orbital myositis” OR “strabismus” OR “Brown’s syndrome” OR “ocular vasculitis” OR “frosted branch angiitis”. Case reports, case series, original research articles, and review articles within the focus on OIDs in FMF were analyzed.

Informed parental consent and institutional committee approval were obtained (#I4-231-20).

Results

Among 512 pediatric patients with FMF, five patients were found to have OIDs: bilateral chronic uveitis in two patients and one patient for each of recurrent orbital myositis (ROM), recurrent optic neuritis (RON), and acquired Brown’s syndrome. All patients received a diagnosis of OIDs during the follow-up of FMF while on colchicine. None had any other associated disease with FMF. All investigations to exclude secondary causes of OID were negative or within normal limits for all of the patients. The demographic and clinical characteristics of patients are presented in Table 1.

Table 1
The demographic and clinical characteristics of patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	Female	Male	Female	Male	Male
Age at FMF onset	6 months	Neonatal	4 years	6 months	18 months
Age at FMF diagnosis	1 year	6 years	5 years	1 year	6 years
Clinical findings of FMF	Recurrent fever, abdominal pain, joint pain	Recurrent fever, abdominal pain, joint pain	Recurrent fever, chest pain, abdominal pain	Recurrent fever, chest pain, joint pain, abdominal pain	Recurrent fever, chest pain, joint pain, arthritis, abdominal pain
MEFV gene mutation	M694V/M680I	M694V/M694V	M694V/M680I	M694V/M694V	M694V/M694V
A family history of FMF	+	+	+	+	+
Parental consanguinity	-	-	+	-	+
Age at OID onset	6 years	8 years	12 years	4 years	8 years
Type of OID	Panuveitis	Anterior uveitis	Orbital myositis	Orbital neuritis	Brown's syndrome
Laterality of OID	Bilateral	Bilateral	Bilateral	Bilateral	Unilateral
Course of OID	Chronic	Chronic	Recurrent	Recurrent	Recurrent
Increase in APRs during OID	No	No	No	Yes	Yes
Autoantibodies	Negative	Negative	Negative	Negative	Negative
HLA testing	Negative	Negative	Negative	Negative	-
Serum ACE level	Normal	Normal	Normal	-	-
Infectious serology*	Negative	Negative	Negative	Negative	Negative
Chest X-ray	Normal	Normal	Normal	Normal	Normal

ACE: Angiotensin-Converting Enzyme, APR: Acute phase reactant, FMF: Familial Mediterranean Fever, MEFV: MEditerranean FeVer, OID: Ocular Inflammatory Disease

* Toxoplasmosis, tuberculosis, syphilis, Lyme disease, cytomegalovirus, herpes simplex virus, rubella, leptospirosis, varicella-zoster virus

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Treatment	Colchicine, topical and systemic steroids, methotrexate, cyclosporine A, adalimumab, infliximab	Colchicine, topical steroids, methotrexate, adalimumab	Colchicine, systemic steroid	Colchicine (dose increased), systemic steroid, anakinra	Colchicine (dose increased), systemic steroid, anakinra
Follow-up duration after diagnosis of OID	5 years	6 years	2 years	4 years	10 years

ACE: Angiotensin-Converting Enzyme, APR: Acute phase reactant, FMF: Familial Mediterranean Fever, MEFV: MEditerranean FeVer, OID: Ocular Inflammatory Disease

* Toxoplasmosis, tuberculosis, syphilis, Lyme disease, cytomegalovirus, herpes simplex virus, rubella, leptospirosis, varicella-zoster virus

Patient 1 and Patient 2 admitted with complaints of pain, redness, and blurred vision in both eyes while FMF was under control on colchicine 1-1.3 mg/m^2/day. Patient 1 was diagnosed with bilateral chronic nongranulomatous panuveitis and treated with topical and systemic steroids, methotrexate for 6 months, adalimumab for 2 years, cyclosporine A in combination with methotrexate and adalimumab for 2 years, and lastly, infliximab for the last 6 months. Despite receiving aggressive treatments, she experienced several recurrences. Patient 2 was diagnosed with bilateral chronic nongranulomatous anterior uveitis. He had bilateral posterior synechiae and peripheral band keratopathy at presentation. He was treated with topical steroids, methotrexate for 3 years, and adalimumab for the last 2 years.

Patient 3 presented with four recurrent episodes of swelling, pain, and redness in both eyes in a year that side differed between the episodes. She did not have fever or any discharge in the eye and she was systemically well on colchicine 1 mg/m^2/day. Due to a suspected diagnosis of orbital cellulitis according to the clinical and imaging findings on computerized tomography, antibiotherapy was initially given for two of the attacks. However, blood cultures resulted in negative and orbital magnetic resonance imaging (MRI) revealed an enlargement of lateral rectus muscle of the right eye at one of the attacks and medial rectus muscle at another (Fig. 1). Then, antibiotherapy was stopped and corticosteroid treatment was initiated with a diagnosis of orbital myositis. Her neurological, ear-throat-nose, and ophthalmological examinations were normal. Thyroid function tests, serum complements C3 and C4, serum immunoglobulins (sIg) G, A, M, and sIgG subgroups were normal in addition to the routine laboratory screening for OIDs. Cranial MRI, abdominal ultrasound, and echocardiography indicated normal findings. Symptoms regressed after the third day of prednisolone that was used by gradual tapering for 6 weeks for two of the episodes. During other ROM episodes, she had mild swelling of the periorbital area for 1–2 days duration that showed spontaneous resolution.

Patient 4 complained of a sudden loss of vision in both eyes, abdominal, and joint pain while he was on colchicine 1.36 mg/m^2/day. He was found to have negative pupillary reflexes and decreased visual acuity in both eyes. Visual evoked potentials (VEP) of both eyes were prolonged. Orbital and cranial MRI with contrast showed bilaterally increased thickness and contrast enhancement of the optic nerve. He was diagnosed with optic neuritis. Cerebrospinal fluid studies were negative for infectious agents and oligoclonal bands. The dose of colchicine was increased after the first episode and intravenous pulse methylprednisolone followed by oral steroids were initiated. On the day of 3, he began to see clearly and VEP control was normal after a month. He experienced two more recurrences in the right eye concomitant with frequent FMF attacks in 2 years. Intravenous pulse methylprednisolone (30 mg/kg/day for 3 subsequent days) and oral steroids were given for a total of one month in each episode. During the third episode of

RON, anakinra was started in addition to systemic steroids due to recurrent ocular inflammatory findings concomitant with typical FMF attacks and he was followed without any symptoms after anti-IL-1 therapy.

Patient 5 applied with sudden-onset strabismus characterized by restriction of elevation and adduction of the left eye while he experienced 1–2 typical FMF attacks per month on colchicine 1.25 mg/m^2/day. A normal physical examination except the abnormalities in eye movements was found with normal visual acuity, pupils, and intraocular pressures. Ocular motility examination was characterized by left hypotropia in primary gaze and elevation deficit above the midline in adduction and straight upward gaze. Forced duction test proved the inability of the elevation of the left eye. Thyroid function tests, serum complements C3 and C4, cranial and orbital MRI with and without contrast were normal. After the diagnosis of acquired Brown's syndrome, the first episode was treated with systemic steroids with an increased dose of colchicine, and ocular movements were returned to normal in a week; however, after experiencing two more recurrences with frequent FMF attacks, anakinra was initiated. Strabismus did not recur after anti-IL-1 therapy.

Discussion

Familial Mediterranean fever is typically described as an autoinflammatory disease that can involve joints, skin, muscles, and kidneys; however, it is a predisposing factor for a variety of different inflammatory diseases involving other organs and systems [17]. Ocular inflammation is an uncommon entity reported in FMF [18]. In this study, five pediatric FMF patients with various OIDs were presented. Although uveitis and optic neuritis have been reported before, to the best of our knowledge, the first cases of ROM and acquired Brown's syndrome observed in patients with FMF in the literature have been introduced [10, 19].

In this study, five cases with an OID among a cohort of 512 pediatric FMF patients seem as a meaningful frequency for the coexistence of both diseases. Although the overall prevalence of ocular inflammatory diseases is not known, the highest prevalence of pediatric noninfectious uveitis reported in the literature (0.03%) is lower than the frequency of uveitis in our cohort (0.39%) [20]. On the other hand, the risk of OID in FMF seems low compared to the frequency of other inflammatory diseases [21]. The etiology of OIDs includes infections, autoimmune, inflammatory, and malignant diseases; however, idiopathic inflammation constitutes the majority of cases [22]. Ocular inflammation has been infrequently observed in FMF and reported OIDs are not unique to this inflammatory syndrome. Besides, other concurrent diseases with FMF such as juvenile idiopathic arthritis or Behçet's disease may complicate the definition of the underlying cause of OIDs. To date, ten cases with uveitis, eight with scleritis, three with optic neuritis, and three with frosted branch angiitis have been reported among OIDs in patients with FMF (Table 2). A recent study indicated foveal vascular abnormalities during an attack-free period in children with FMF whereas increased choroidal thickness with a significant correlation of C-reactive protein was found during an acute FMF attack in another study [23, 24]. In this study, investigations to find out the etiology of the diagnosed OID excluded all known secondary causes of OIDs. None of the patients had any other associated disease with FMF. Ocular inflammation was bilateral in four of the cases and all OIDs had recurrent and chronic courses. Moreover, one of the patients with uveitis had bilateral panuveitis that is an infrequent type of pediatric uveitis [25]. In two of the patients, typical FMF attacks and recurrences of OIDs were temporally associated. Based on these observations and case series in the literature, we may postulate that OIDs observed in FMF patients may be associated with increased inflammation of FMF. Substantial overlap between pathogenic mechanisms of both diseases seems possible.

Table 2
Summary of patients with familial Mediterranean fever concurrent with ocular inflammatory diseases in the medical literature

Author, year [reference]	No. of patients	Mutation	Type of OID (no. of patients)	Course of OID (no. of patients)	Other concurrent inflammatory diseases (no. of patients)	Treatment (no. of patients)
Yazici, 1982 [30]	1	Unknown	Anterior uveitis and episcleritis	Recurrent	None	Colchicine, NSAIDs, systemic and topical steroids
Scharf, 1985 [31]	2	Unknown	Episcleritis	One episode defined (2/2)	None	Colchicine, NSAIDs, topical steroids
Hirsh, 1990 [32]	1	Unknown	Panuveitis	Recurrent	None	Colchicine (dose increased), systemic and topical steroids, surgery
Lossos, 1993 [19]	2	Unknown	Optic neuritis	One episode defined (2/2)	None	Colchicine, systemic steroids (1)
Akman, 2001 [9]	2 (siblings)	Unknown	Panuveitis (1) Episcleritis (1)	Recurrent	None	Colchicine, NSAIDs, systemic and topical steroids, photocoagulation (1)
Ozaltin, 2001 [13]	1	M694V/M694V	Anterior uveitis	One episode defined	None	Colchicine
Berestizschevsky, 2008 [12]	1	Unknown	Episcleritis	One episode defined	None	Colchicine (dose increased), NSAIDs, systemic and topical steroids, mitomycin C, surgery
Akalin, 2010 [27]	1	M694V/M694V	Episcleritis	One episode defined	None	Colchicine, systemic and topical steroids
Satoh, 2010 [33]	1	Unknown	Frosted branch angiitis	One episode defined	None	Colchicine, systemic steroids

NSAID: Nonsteroidal Anti-Inflammatory Drug, OID: Ocular Inflammatory Disease

Author, year [reference]	No. of patients	Mutation	Type of OID (no. of patients)	Course of OID (no. of patients)	Other concurrent inflammatory diseases (no. of patients)	Treatment (no. of patients)
Yazici, 2014 [10]	6	Unknown	Anterior uveitis (2) Posterior uveitis (2) Intermediate uveitis (1) Posterior scleritis (1)	Recurrent or chronic (5/6)	Behçet's disease (2)	Colchicine, systemic and topical steroids, methotrexate (1), mitomycin C (1), cyclosporine A (2), photocoagulation (2), surgery for cataract (2)
Petrushkin, 2015 [29]	1	Unknown	Intermediate uveitis	One episode defined	None	Colchicine (dose increased)
Basaran, 2016 [14]	1	M694V/M694V	Optic neuritis	Recurrent	None	Colchicine (dose increased), systemic steroids, anakinra, kanakinumab
Ozates, 2016 [11]	1	M694V/M694V	Frosted branch angiitis	Recurrent	None	Colchicine, systemic steroids, azathioprine, laser
Chan, 2018 [34]	1	V726A	Frosted branch angiitis	One episode defined	None	Colchicine, systemic steroids
Mansour, 2019 [35]	1	Unknown	Posterior scleritis	One episode defined	None	Colchicine, systemic steroids

NSAID: Nonsteroidal Anti-Inflammatory Drug, OID: Ocular Inflammatory Disease

Previous studies have thoroughly studied the genotype and phenotype correlation in FMF and shown that identified mutations do not always correlate with the clinical manifestations. On the other hand, carrying M694V mutation has been associated with a relatively severe disease course, an early disease onset, and a higher risk for concomitant diseases [26, 27]. Strikingly, M694V mutation has been the most frequently reported mutation in patients with FMF and OIDs in the literature [11, 13, 14, 28]. However, although the role of several inflammasomes has been discovered in the pathogenesis of several OIDs, the pyrin inflammasome has not been shown to be involved in any OIDs to date [29]. In the current study, all patients presented with typical FMF attacks at early ages and carried at least one M694V mutation.

Colchicine may not be effective in associated inflammatory diseases with FMF such as sacroiliitis and vasculitis and additional therapies to colchicine are usually needed [5, 27]. In the literature, several studies and case reports presented that topical and systemic corticosteroids and other immunosuppressants in addition to colchicine were needed to control ocular inflammation in FMF patients because of their recurrent and chronic courses (Table 2). Some rare instances recovered by regular use or an increased dose of colchicine [13, 30]. Similar to the literature, all of our patients experienced OIDs while on colchicine. Although three of them benefitted from systemic corticosteroids during the acute presentation of OID, ocular inflammation recurred after the withdrawal of steroids. An increased dose of colchicine and the addition of anti-IL-1 therapy in two of them provided a long-term remission. Unfortunately, both patients with uveitis experienced several recurrences and ocular complications despite the use of different immunosuppressants.

Limitations of our study could be its retrospective nature. Future multi-centered studies involving larger numbers of FMF patients may help to examine possible associations between FMF and ocular inflammation. Moreover, molecular studies for the identification of pathogenic pathways linking FMF to OIDs need further investigations.

In conclusion, there is insufficient data to indicate whether FMF is a disease that causes ocular inflammation. However, increased frequency of OIDs in FMF as per the pediatric population and relapsing and chronic course of OIDs occasionally with concurrent FMF attacks suggest that this inflammatory syndrome especially those carrying M694V mutations may be a predisposing factor for OIDs. Any ocular symptoms in patients with FMF should alert physicians for the coexistence of OIDs. Because OIDs are not specific for FMF, all possible underlying causes should be excluded.

Declarations

Conflict of interest: None

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Figures

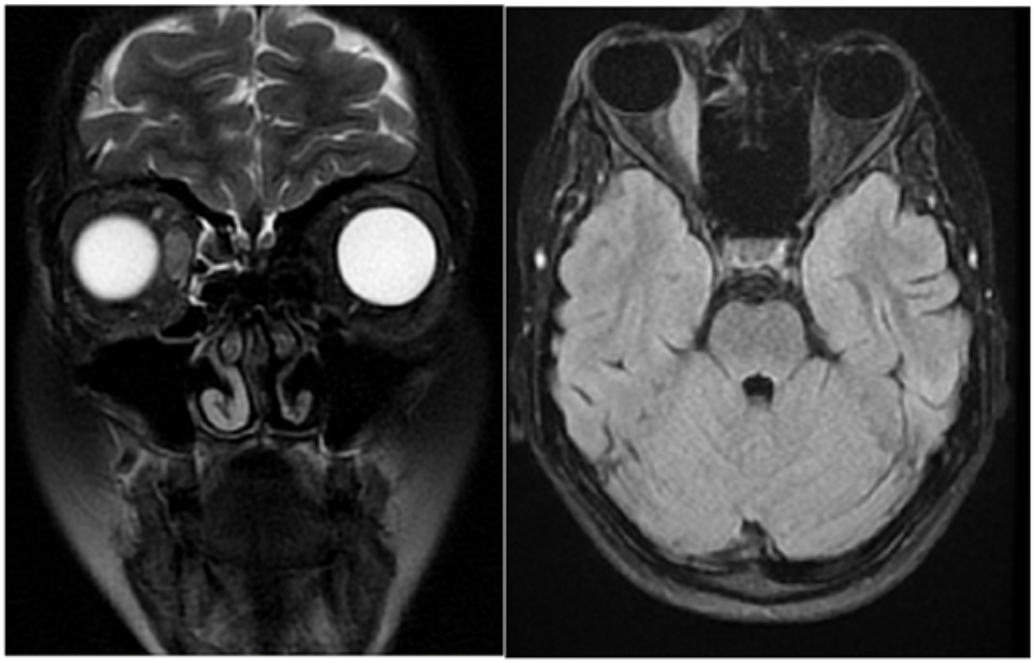

Figure 1

Magnetic resonance imaging of the patient with familial Mediterranean fever and recurrent orbital myositis