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

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Abstract

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

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

Results Among 512 pediatric patients with FMF, five cases were found to have OIDs: bilateral anterior chronic uveitis, bilateral panuveitis, recurrent optic neuritis (RON), recurrent orbital myositis (ROM), and acquired Brown’s syndrome. The first cases of ROM and acquired Brown’s syndrome in FMF have been described in the literature. All cases 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.

Keywords Familial Mediterranean fever · Ocular inflammatory diseases · Orbital myositis · Orbital neuritis · Uveitis

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. The gain-of-function mutations in the MEFV gene induce hyperinflammation through the pyrin inflammasome [1]. Typical clinical presentation is recurrent spontaneously resolving episodes of fever and polyserositis (peritonitis, pleuritis, pericarditis, and synovitis) that last between 1 and 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 colchicine resistance or intolerance [4].
Besides hyperinflammatory state in FMF attacks, some patients, especially those carrying exon 10 mutations, experience persistent subclinical inflammation and a tendency to other inflammatory diseases that are parts of the heterogeneous disease spectrum of FMF [5]. The association 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 a coexistence of different clinical entities [6–8]. Previous studies 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 study possible relations between these two inflammatory entities. Further, the medical literature on OIDs reported in patients with FMF was reviewed.

Material and methods

Demographic and clinical data were extracted from the electronic medical records of patients with FMF and OIDs followed in the Department of Pediatric Rheumatology of Ankara University School of Medicine in the last 5 years (January.2016–January.2021). 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 ophthalmologic 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, antinuclear antibodies (ANA), human leukocyte antigen (HLA) testing, serum angiotensin-converting enzyme (ACE) level, and a chest X-ray were carried out to investigate the etiology of OIDs. Serology tests to detect tuberculosis, hepatitis, toxoplasmosis, syphilis, Lyme disease, cytomegalovirus, herpes simplex virus, rubella, leptospirosis, and varicella-zoster virus were used. Cranial magnetic resonance imaging (MRI) 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 observed in FMF patients were analyzed.

Informed parental consent and ethics committee approval by Ankara University Faculty of Medicine Human Research Ethics Committee (#I4-231–20) were obtained.

Results

Among 512 pediatric patients with FMF, five cases were found to have OIDs: bilateral anterior chronic uveitis, bilateral panuveitis, recurrent optic neuritis (RON), recurrent orbital myositis (ROM), and acquired Brown’s syndrome. All cases 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 found negative or within normal limits for all of the cases. Moreover, there were no signs of colchicine toxicity. The demographic and clinical characteristics of cases are presented in Table 1.

Case 1: The patient admitted with complaints of pain, redness, and blurred vision in both eyes while...
|                | Case 1                  | Case 2                  | Case 3                  | Case 4                  | Case 5                  |
|----------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| **Gender**     | Female                  | Male                    | Male                    | Female                  | Male                    |
| **Age at FMF onset** | 6 months               | Neonatal                | 6 months                | 4 years                 | 18 months               |
| **Age at FMF diagnosis** | 1 year                 | 6 years                 | 1 year                  | 5 years                 | 6 years                 |
| **Clinical findings of FMF** | Recurrent fever, abdominal pain, joint pain | Recurrent fever, abdominal pain, chest pain, joint pain | Recurrent fever, chest pain, abdominal pain | Recurrent fever, chest pain, joint pain, arthritis, abdominal pain |
| **MEFV gene mutation** | M694V/M680I            | M694V/M694V             | M694V/M694V             | M694V/M680I             | M694V/M694V             |
| **A family history of FMF** | +                      | +                       | +                       | +                       | +                       |
| **Parental consanguinity** | –                     | –                       | –                       | +                       | +                       |
| **Age at OID onset** | 6 years                | 8 years                 | 4 years                 | 12 years                | 8 years                 |
| **Type of OID** | Panuveitis              | Anterior uveitis        | Optic neuritis          | Orbital myositis        | Brown’s syndrome        |
| **Laterality of OID** | Bilateral              | Bilateral               | Bilateral               | Bilateral               | Unilateral              |
| **Course of OID** | Chronic                 | Chronic                 | Recurrent               | Recurrent               | Recurrent               |
| **Increase in APRs at the time of OID** | No                     | No                      | Yes                     | No                      | Yes                     |
| **Serum ANA test** | Negative                | Negative                | Negative                | Negative                | Negative                |
| **HLA testing** | Negative                | Negative                | Negative                | Negative                | –                       |
| **Serum ACE level** | Normal                  | Normal                  | Normal                  | Normal                  | –                       |
| **Infectious serology** | Negative               | Negative                | Negative                | Negative                | Negative                |
| **Chest X-ray** | Normal                  | Normal                  | Normal                  | Normal                  | Normal                  |
| **Treatment** | Colchicine, topical and systemic steroids, methotrexate, cyclosporine A, adalimumab, infliximab | Colchicine, topical steroids, methotrexate, adalimumab | Colchicine (dose increased), systemic steroid, anakinra | Colchicine, systemic steroid | Colchicine (dose increased), systemic steroid, anakinra |
| **Follow-up duration after diagnosis of OID** | 5 years                | 6 years                 | 4 years                 | 2 years                 | 10 years                |

ACE: Angiotensin-Converting Enzyme, ANA: Antinuclear Antibodies, APR: Acute Phase Reactant (C-reactive protein, erythrocyte sedimentation rate), FMF: Familial Mediterranean Fever, HLA: Human Leukocyte Antigen, MEFV: MEditerranean FeVer, OID: Ocular Inflammatory Disease

*Toxoplasmosis, tuberculosis, hepatitis, syphilis, Lyme disease, cytomegalovirus, herpes simplex virus, rubella, leptospirosis, varicella-zoster virus
FMF was under control on colchicine 1 mg/m²/day. She 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.

**Case 2:** The patient was diagnosed with bilateral chronic nongranulomatous anterior uveitis after his admission with pain and redness in both eyes. His FMF was well controlled on colchicine 1.3 mg/m²/day. He had bilateral posterior synechiae and peripheral band keratopathy at the diagnosis. He was treated with topical steroids, methotrexate for 3 years, and adalimumab for the last 2 years.

**Case 3:** The patient complained of sudden loss of vision in both eyes, abdominal and joint pain while he was on colchicine 1.4 mg/m²/day. Pupillary reflexes were absent and visual acuity was decreased in both eyes. Visual evoked potentials (VEP) of both eyes showed prolonged latency. 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 was 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. Three days later, he began to see clearly while 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.

**Case 4:** The patient presented with four recurrent episodes of periorbital 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/m²/day. Systemic examination findings were normal without muscle weakness or skin rash. Her ear-nose-throat and ophthalmological examinations were normal. 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 negative and orbital 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. Thyroid function tests, serum muscle enzymes, complements C3 and C4, immunoglobulins (sIg) G, A, M, and sIgG subgroups were normal in addition to the routine laboratory screening for OIDs. Antibodies to extractable nuclear antigens (ENA) and PR3 and MPO anti-neutrophil cytoplasmic antibodies (ANCA) were found negative. Cranial MRI, abdominal ultrasound, and echocardiography indicated normal findings. Symptoms regressed after the third day of prednisolone that was later tapered in 6 weeks for two of the episodes. During other RON episodes, she had mild periorbital swelling for 1–2 days duration that showed spontaneous resolution.

**Case 5:** The patient consulted with sudden-onset strabismus characterized by restriction of elevation and adduction of the left eye. A typical FMF attack accompanied and the patient experienced frequent FMF attacks while on colchicine 1.25 mg/m²/day. Systemic examination was normal without any findings of muscle weakness or skin involvement. Ocular motility examination was characterized by left hypotropia in primary gaze and elevation deficit above the midline in adduction and straight upward gaze. The forced duction test proved the inability of the elevation of the left eye. Pupillary responses and intraocular pressures were found normal with a visual acuity of 10/10. Thyroid function tests, serum complements C3 and C4, muscle enzymes, 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 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.
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 [10]. 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 described [13, 18]. In this study, five cases with an OID among a cohort of 512 pediatric FMF patients suggest a meaningful frequency for the coexistence of both diseases. Although the overall prevalence of OIDs 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%) [19]. On the other hand, the risk of OID in FMF seems low compared to the frequency of other inflammatory diseases [20]. The etiology of OIDs includes infectious, autoimmune, inflammatory, and malignant diseases; however, idiopathic inflammation constitutes the majority of cases [21]. 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 significantly correlated with C-reactive protein was found during acute FMF attacks in another study [22, 23]. In this study, investigations to find out the etiology of the diagnosed OID excluded all known secondary causes. None of the patients had any other associated diseases 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 [24]. 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 appears possible. 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
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 (no. of patients) | Type of OID | Course of OID (no. of patients) | Other concurrent inflammatory diseases (no. of patients) | Treatment (no. of patients) |
|--------------------------|-----------------|-----------------------------|-------------|-------------------------------|--------------------------------------------------------|-----------------------------|
| Yazici, 1982 [28]        | 1               | Unknown                     | Anterior uveitis and episcleritis | Recurrent | None | Colchicine, NSAIDs, systemic and topical steroids |
| Scharf, 1985 [29]        | 2               | Unknown                     | Episcleritis | One episode defined (2/2) | None | Colchicine, NSAIDs, topical steroids |
| Hirsh, 1990 [30]         | 1               | Unknown                     | Panuveitis | Recurrent | None | Colchicine (dose increased), systemic and topical steroids, surgery |
| Lossos, 1993 [18]        | 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 [25]        | 1               | M694V/M694V                 | Episcleritis | One episode defined | None | Colchicine, systemic and topical steroids |
| Satoh, 2010 [31]         | 1               | Unknown                     | Frosted branch angiitis | One episode defined | None | Colchicine, systemic steroids |
| Yazici, 2013 [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), photoocoagulation (2), surgery for cataract (2) |
| Petrushkin, 2015 [27]    | 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 |
Hand, carrying M694V mutation has been associated with a relatively severe disease course, an early disease onset, and a higher risk for concomitant diseases [25, 26]. Strikingly, M694V mutation has been the most frequently reported mutation in patients with FMF and OIDs in the literature [11, 13, 14, 25]. 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. 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 are usually needed [6, 26]. 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 [12, 27]. 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 patients provided a long-term remission. Unfortunately, both patients with uveitis experienced several recurrences and ocular complications despite the use of different immunosuppressants.

The limitations of our study could be its retrospective nature. Future multicentered 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 are 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 to FMF, all possible underlying causes should be excluded.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Parental informed consent and institutional ethical approval (Ankara University Faculty of Medicine Human Research Ethics Committee, #14-231-20) were obtained.
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