**ORIGINAL ARTICLE**

# Ophthalmic manifestations in familial Mediterranean fever: a case series of 6 patients

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**Purpose:** *To describe the ocular involvement of patients with familial Mediterranean fever (FMF) followed in a tertiary referral center.*
**Methods:** *The data of 6 patients with FMF were retrospectively reviewed. Detailed ophthalmologic examinations, type of inflammation, course of the disease, number of recurrences, treatment regimens, complications, and comorbid ocular or systemic diseases were noted.*
**Results:** *The mean age ± SD at diagnosis was 29.3 ± 19.3 (4-53) years. A total of 66.7% of the patients were male and 66.7% of the patients had bilateral disease. The anatomical distribution of the ophthalmic involvement was as follows: posterior uveitis in 2 (33.3%), anterior uveitis in 2 (33.3%), posterior scleritis in 1 (16.7%), and intermediate uveitis in 1 (16.7%) patient. The course was recurrent in 50% of the patients. Final visual acuities were favorable except in the patients with chronic course uveitis. Cystoid macula edema, epiretinal membrane, retinal ischemia, cataract, glaucoma, and band keratopathy were complications noted in the follow-up period. Both cataract and glaucoma patients (50%) needed a surgical intervention. In 33.3% of patients, Behçet disease was present as a concurrent disease. In patients with posterior uveitis and the patient with intermediate uveitis (50%), systemic immunosuppression was required.*
**Conclusions:** *There was a male and bilateral involvement predominance. The course of the inflammation was recurrent in half of the patients. Since ocular involvement in FMF is very rare, it should be considered as diagnosis of exclusion.*

**Keywords:** *Behçet disease, Familial Mediterranean fever, Scleritis, Uveitis*

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## INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessively inherited autoinflammatory disorder characterized by recurrent episodes of febrile serositis like peritonitis and pleuritis (1). It is frequently seen in Jewish (1/500), Armenian (1/500), Turkish (1/1000), and Arabic ethnicities (1/25) (2-4). The most important problem in this disease is amyloidosis leading to renal failure (5). In most patients, colchicine treatment is enough to prevent this complication. In the pathophysiology, a mutation of the *MEFV* gene located on the 16$^{th}$ chromosome causes defective functioning pyrin protein, which has an autoregulatory role in inflammatory cascades of neutrophil activation and proinflammatory cytokine release (1).Many systems may be involved in FMF but the eye is rarely a target of this inflammatory disease. Ocular involvement was first reported by Michaelson et al in 1959 (6) as retinal colloid bodies. Then a few case reports including episcleritis, anterior uveitis, and panuveitis were published (5, 7, 8). It is unclear why FMF rarely causes ophthalmic manifestations, compared to some autoinflammatory diseases that have ocular involvement in the vast majority of patients (9).

We discuss the clinical characteristics of inflammatory ocular involvement in 6 patients with FMF who were followed in a tertiary referral center. To our knowledge, this is the only case series of ophthalmic manifestations in FMF.

## MATERIALS AND METHODS

Institutional review board and ethics committee approval was obtained prior to the study. The archive of our tertiary referral center's uvea division consisting of 1265 uveitis patients was reviewed and the data of 6 patients with FMF diagnosis were gathered. Age at first presentation, sex, follow-up length, anatomic location, clinical course, family history, characteristics of ocular involvement, concomitant ocular or systemic morbidities, number of recurrences, complications, performed ophthalmic surgeries, and treatment regimens were recorded. Detailed ophthalmologic examinations including best-corrected visual acuity (BCVA) gathered with Snellen charts, intraocular pressure, slit-lamp biomicroscopy, and dilated fundus examinations were performed. Fundus fluorescein angiography, ultrasonography, and optical coherence tomography were performed when indicated. Routine laboratory evaluation consisted of a complete blood count with differential, biochemical analysis, urinalysis, and erythrocyte sedimentation rate. Antinuclear antibody, rheumatoid factor, C-reactive protein, human leukocyte antigen typing, angiotensin-converting enzyme, pathergy test, skin tuberculin test, chest radiography, syphilis, toxoplasma, herpes, and Lyme serology were done in selected patients. Anatomic location and course of the disease were classified according to Standardization of Uveitis Nomenclature working group criteria (10). Anatomically, uveitis was classified as anterior, intermediate, posterior, or panuveitis. Inflammation lasting less than 3 months was defined as acute uveitis, relapsing episodes separated by periods of inactivity without treatment for 3 months was defined as recurrent, and inflammation lasting longer than 3 months was defined as chronic uveitis. Two of 6 patients received the FMF diagnosis from a rheumatology clinic before ocular involvement, and the rest were diagnosed during the etiologic investigation of their ophthalmic inflammation. Definite FMF diagnosis was based on diagnostic criteria of Tel Hashomer, which is one of the most commonly used criteria in the clinical diagnosis of FMF (11). According to these criteria, definite diagnosis requires 2 major or 1 major and 2 minor criteria, whereas probable diagnosis requires 1 major and 1 minor. Major criteria are 1) recurrent febrile episodes accompanied by peritonitis, synovitis, or pleuritis; 2) amyloidosis (secondary amyloidosis: AA type amyloidosis) of the AA type without predisposing disease; and 3) favorable response to continuous colchicine treatment. Minor criteria are 1) recurrent febrile episodes; 2) erysipelas-like erythema; and 3) FMF in a first-degree relative. The study adhered to the tenets of the Declaration of Helsinki.

## RESULTS

The mean age ± SD at diagnosis was 29.3 ± 19.3 (4-53) years. Mean follow-up time was 28.8 ± 19.6 (3-58) months. A total of 66.7% (4/6) of patients had bilateral disease and 66.7% (4/6) were male. The anatomic distribution of the ophthalmic involvement was as follows: posterior uveitis in 2 (33.3%), anterior uveitis in 2 (33.3%), posterior scleritis in 1 (16.7%), and intermediate uveitis in 1 (16.7%) patient. The clinical course was acute in 1, recurrent in 3 (50%), and chronic in 2 patients.

One of the anterior uveitis patients was a 43-year-old woman who presented with bilateral iridocyclitis with posterior synechiae and medium-sized keratic precipitates (KPs) in Arlt's triangle. She was receiving oral colchicine for the treatment of the systemic disease. The patient had 3 recurrent anterior uveitis attacks, all treated with topical and oral steroids in addition to her ongoing oral colchicine treatment. The patient developed cataract and was treated with uneventful cataract surgery, gaining a final BCVA of 1.0. The second anterior uveitis patient was a 10-year-old boy presenting with bilateral nongranulomatous medium-sized KPs located in Arlt's triangle. Topical steroid added to continuous oral colchicine treatment regimen was sufficient to control the inflammation in all 3 attacks and to preserve the BCVA of 1.0. This patient was known to have the diagnosis of FMF at presentation. Additionally, he was diagnosed with Behçet disease during the follow-up period.

In a 14-year-old boy, the presentation was as acute posterior scleritis in his left eye. The patient was treated with 3 days of intravenous pulse methylprednisolone (1 g/d) followed by oral prednisolone of 1 mg/kg with gradual tapering. His BCVA improved from 0.1 to 1.0. Neither recurrences nor complications occurred in this patient.

Intermediate uveitis was seen in the left eye of a 7-year-old boy with a chronic clinical course. He was treated with topical and oral steroids and methotrexate (7.5-12.5 mg

weekly) in addition to ongoing oral colchicine treatment. Although he received aggressive treatment, this patient had 6 recurrences and developed cataract, glaucoma, and band keratopathy. For glaucoma that could not be controlled with medical treatment, trabeculectomy with mitomycin-C was performed. Intraocular pressure was controlled postoperatively via timolol maleate and dorzolamide fixed combination. Phacoemulsification and intraocular lens implantation surgery was performed and the patient needed a laser capsulotomy intervention for secondary capsular opacification. His final BCVA was 0.3.

A 19-year-old woman and a 53-year-old man presented with bilateral posterior uveitis. The woman had a chronic course with 2 recurrent episodes of bilateral vitritis and retinal vasculitis. She had developed snowball opacities, cystoid macular edema, epiretinal membrane formation, and neovascularization elsewhere. This patient required systemic immunosuppressive treatment (cyclosporine-A 2-5 mg/kg) in addition to topical and oral steroids and colchicine. Bilateral panretinal photocoagulation was also performed for neovascularizations. Final BCVA was 0.2 and 0.3 for the right and left eyes, respectively. The systemic investigation of uveitis etiology did not reveal any disorder other than the present FMF diagnosis. After the second attack, the patient developed systemic signs of Behçet disease and was referred to rheumatology again. With the newly developed signs, the patient fulfilled the diagnostic criteria (12) and received a Behçet disease diagnosis. The male patient had bilateral vitritis and retinal vasculitis with a recurrent course leading to complications like cystoid macular edema, epiretinal membrane formation, and retinal vein occlusion. Final BCVA was 1.0 in both eyes. The treatment for this patient was the same as for the other posterior uveitis patient. A summary of all cases presented is shown in Table I.

## DISCUSSION

Autoinflammatory diseases are a group of rare disorders characterized by recurrent unprovoked inflammatory episodes without any high titers of autoantibodies (13). Familial Mediterranean fever is classified under this group along with neonatal onset multisystem inflammatory disease, Muckle-Wells syndrome, familial cold autoinflammatory syndrome, TNF receptor-1–associated periodic syndrome, and Blau syndrome. This particular disease presents with recurrent abdominal pain, pleurisy, arthritis, erysipelas-like skin lesions, and neutrophil dominance in blood count. The *MEFV* mutation described in FMF was the first identified mutation responsible for an autoinflammatory syndrome. However, authors claim that *MEFV* gene, rather than being unique to FMF, should be considered as a predisposition to inflammatory processes since its prevalence was also found to be increased in Henoch-Schonlein purpura, polyarteritis nodosa, Behçet disease, and other vasculitis (13).

**TABLE I -** DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS

| | **Patient 1** | **Patient 2** | **Patient 3** | **Patient 4** | **Patient 5** | **Patient 6** |
|---|---|---|---|---|---|---|
| Age, y | 14 | 10 | 43 | 7 | 19 | 53 |
| Sex | Male | Male | Female | Male | Female | Male |
| Ophthalmic manifestation | Posterior scleritis | Anterior uveitis | Anterior uveitis | Intermediate uveitis | Posterior uveitis | Posterior uveitis |
| Laterality | Unilateral | Bilateral | Bilateral | Unilateral | Bilateral | Bilateral |
| Course | Acute | Recurrent | Recurrent | Chronic | Chronic | Recurrent |
| Complications | - | - | Cataract | Cataract, glaucoma, band keratopathy | CME, ERM, NVE | CME, ERM, BRVO |
| Final BCVA | 1.0 | 1.0/1.0 | 1.0/1.0 | 0.3 | 0.2/0.3 | 1.0/1.0 |
| Concomitant diseases | - | Behçet disease | - | - | Behçet disease | - |

BRVO = branch retinal vein occlusion; CME = cystoid macular edema; ERM = epiretinal membrane; NVE = neovascularization elsewhere.

In FMF, ophthalmic involvement is rare and nonspecific, in contrast to other autoinflammatory disorders, and has been documented as case reports of episcleritis, anterior uveitis, panuveitis, and retinal colloid bodies (9). The first report about the ocular involvement of FMF was from Michaelson et al (6), documenting retinal colloid bodies in 56% of their Jewish patients compared to 11% in non-Jewish patients. However, upcoming studies revealed that this finding was only seen in 8% of patients with FMF and consequently ophthalmic manifestations were dropped from the clinical criteria and even accepted as a finding to rule out the diagnosis (5).

The mean age at diagnosis of our patients was 29.3 ± 19.3 years, which is higher than expected, since in most patients with FMF the diagnosis was confirmed before age 20 (13). It is also important to note that a patient who got FMF diagnosis at age 66 years has been previously reported (14). The relatively higher mean age in our group was due to 2 patients who were 43 and 53 years old. Other patients received the FMF diagnosis and ocular involvement before age 20. In the literature, although most patients with ocular involvement were in the 1st and 2nd decades, some had also presented at the 4th and 5th decade (5, 7). Clinicians should keep this disease in mind especially in young patients but in older patients also.

The reported male to female ratio in patients with FMF was 1:1 to 2:1 (15, 16). In our group, this ratio was 2:1, which is comparable to the literature. Although there are no comparable data, ocular involvement was bilateral in 66.7% of the patients.

Since FMF has a recurrent nature, it is not surprising that the ocular inflammation in our series had a recurrent course in 50%. Anatomically, patients with recurrent ocular inflammation had either posterior or anterior uveitis. The only case with acute clinical course was the posterior scleritis patient in whom no recurrence was seen with proper treatment. The chronic cases were posterior and intermediate uveitis patients who also had the worst final BCVAs (0.2-0.5) due to several complications like cystoid macular edema, epiretinal membrane, glaucoma, cataract, and band keratopathy. The chronic posterior uveitis patient fulfilled the diagnostic criteria of Behçet disease during the follow-up period, which may explain the treatment-resistant chronic course.

Episcleritis was the most commonly reported ophthalmic manifestation of patients with FMF in the literature (1, 5, 12, 17). Scleritis, however, was only reported in a 43-year-old man with a concomitant sudden hearing loss (18). Scleritis is a potentially sight-threatening ocular disease that is often associated with life-threatening systemic illness (19). The frequency of associated systemic disorders like rheumatoid arthritis, Wegener granulomatosis, seronegative spondyloarthropathies, relapsing polychondritis, and systemic lupus erythematosus differs from 36% to 57% (20, 21). Both scleritis and FMF are closely associated with systemic vasculitis like Henoch-Schonlein purpura, Polyarteritis nodosa, and Wegener granulomatosis. The only reported case of scleritis also had a sudden sensory hearing loss in which vasculitis was also blamed in the pathogenesis (22, 23). In our case with scleritis, we could not find any underlying or accompanying disease except for FMF.

The anterior uveitis in our patients was nongranulomatous with recurrent course. The recurrent uveitis episodes caused complications like posterior synechiae and cataract in one of the cases in whom oral steroid was needed to get the inflammation under control. As mentioned, FMF may be associated with several diseases. In the adult population, ankylosing spondylitis and other spondyloarthritis, which are common causes of anterior uveitis, were reported to have a close connection with FMF (10). Juvenile idiopathic arthritis, the most common cause of childhood anterior uveitis (24), was also reported to be seen together with both FMF and ankylosing spondylitis (25). For this reason, we investigated and referred all our patients to rheumatology and related departments for the presence of any other autoimmune and autoinflammatory syndromes. One of the anterior uveitis patients also developed Behçet disease in the follow-up period. As mentioned above, there is a close relationship between FMF and Behçet disease (13). This patient and the previously mentioned patient with posterior uveitis provide an example of the coexistent appearance of these 2 diseases.

Literature search revealed no intermediate uveitis cases in FMF. Our 7-year-old patient had unilateral chronic intermediate uveitis and presented with BCVA of 0.5, which decreased to final BCVA of 0.3. This decrease might be attributable to severe complications like cataract, glaucoma (both needed surgery), and band keratopathy. Although steroid-sparing treatment with methotrexate was started, the patient required a concomitant steroid treatment for a long time, which may play an additive role for the development of complications. A specific underlying etiology could not be found in 75% of intermediate uveitis cases, and these cases were accepted as idiopathic. One

of the most common diseases causing intermediate uveitis is multiple sclerosis (26). Yahalom et al (27) revealed that multiple sclerosis was more common in patients with FMF than in the general Israeli population and *M694V* homozygotic mutation might cause patients with FMF to develop multiple sclerosis. Since FMF-related intermediate uveitis was not reported previously and there are some diseases that may cause intermediate uveitis and are reported to have higher frequencies of FMF association, our patient was investigated extensively for the presence of other associated diseases. Clinical examination and radiologic and laboratory investigations did not reveal any other pathology or coexistent diseases. We suggest that FMF be kept in mind in patients with intermediate uveitis in whom an underlying disease has not been found.

Posterior uveitis was seen in 2 of 6 patients. To our knowledge, as with intermediate uveitis, there has been no posterior uveitis reported in FMF. In our patients, there were both retinal vasculitis and vitritis, which caused cystoid macular edema and epiretinal membrane formation. Additionally, the vasculitic nature of the disease caused vascular occlusions and resulted in severe ischemia that resulted in retinal neovascularization in one of the patients. In both patients we were obliged to use systemic immunosuppressive medication to control the inflammation. In the patient with concurrent Behçet disease, final BCVA was limited due to the aggressive course of the disease that resulted in neovascularization. In this patient, although the presentation and the clinical course of the disease were compatible with Behçet disease, the definitive diagnosis could not be made according to the diagnostic criteria of the International Study Group for Behçet Disease (12). With further findings leading to Behçet disease diagnosis, the cause of the uveitis in this patient might be shifted to Behçet disease from FMF. Since the only confirmed etiology was FMF at the time of the uveitis attack, the patient was included in the study. Additionally, this case was considered as a valuable example showing that the diagnosis may change throughout the follow-up and FMF may be associated with Behçet disease.

The first panuveitis patient reported in the literature was a 19-year-old Sephardic Jewish man with bilateral involvement leading to retinal tear in one eye, which required encirclement surgery (8). The second panuveitis case was an 11-year-old Turkish girl, who also presented with bilateral involvement and who had retinal tear treated with prophylactic laser photocoagulation (7). We did not have a patient with panuveitis in our series. As mentioned before, the most commonly reported ophthalmic manifestation of FMF was episcleritis, which we did not observe in our series (5). This fact can be explained by the tertiary referral pattern of our center. We have a limited chance to see uncomplicated simple episcleritis cases as they are mostly diagnosed and treated in primary care centers. Another reason is that our center is a specialized eye hospital without pediatrics or internal medicine departments. Therefore, we do not have the opportunity to see patients referred from these departments for these types of eye problems.

In conclusion, ocular involvement of FMF should be considered as a diagnosis of exclusion after all possible underlying causes are eliminated. In our patient series, there was a male and bilateral involvement predominance. Although episcleritis is the most common form of ophthalmic inflammation in FMF, as previously reported, clinicians should remember that the disease may also present with scleritis, anterior-intermediate-posterior, and panuveitis. The disease shares common pathophysiologic pathways with some of the immune-mediated diseases, so patients should be examined for these diseases.

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