Flares—attacks—episodes

Flare episodes usually last between 1-4 days, while other symptoms may last as long as 7 days. The duration and severity of these episodes can be variable to the patient, as a fever may occur prior, during, after, or independently of other flare symptoms i.e. GI issues, joint swelling, rashes, etc (see symptoms section). Some patients will NOT present with any fevers. There are atypical cases where patients are afebrile (normal temperature) or even have mild hypothermia. Patients may present with either one or many symptoms during an attack or they may be spread out over several days. For example, a patient may present with a high fever during day 1 and 2, stomach pain on day 3 and joint pain on days 4-6. Another example would be a patient who presents with all of these symptoms including a fever for 4 days at a time. A third example would be a patient who presents with a variety of symptoms but has NO fever. NO two patients will present in the same way, much less, flare symptoms may change over time. Additionally, in FMF families where several members are affected, the individuals may not have similar symptom patterns.

Flare presentation with any combination of symptoms may occur as often as weekly or as infrequently as a few times per year. The frequency of flares depends upon treatment, treatment efficacy, the age of onset, genetic variability, and other factors. Moreover, some patients may have remission periods lasting months or even years.

There are FMF cases where patients present with clinical symptoms but will NOT present with elevated inflammatory markers (CRP, ESR, WBC) in or out of flaring. This may be due to other elevated inflammatory biomarkers that are not typically tested nor are commercially available, or for other unknown reasons.

Photo by MART PRODUCTION

GI manifestations

Ninety five percent (95%) of patients experience abdominal pain. It may be accompanied by constipation, diarrhea or both. These attacks are unpredictable and often happen spontaneously without any type of physical trigger or may be caused by environmental temperature, physical activity, certain foods, emotional stress (positive and negative), etc. It is not uncommon for pain to originate from one area and spread throughout the abdominal region. It can be characterized as cramp-like, stabbing, colicky, rigid, bloating, and shooting from the lower back to the front (resembling kidney pain).

The pain is variable, while some patients can manage their gastrointestinal symptoms with NSAIDs (e.g. ibuprofen, acetaminophen), oral steroids or opioids. Emergency room interventions including IV pain control, IV steroids, and fluid replenishment (due to diarrhea/vomiting) may be necessary.

An intestinal obstruction due to massive inflammation should be ruled out. The pain of the abdominal attack may be so severe that it is often thought to be appendicitis, when it is diagnostically peritonitis. It is critical that doctors rule out appendicitis via an ultrasound or scan to avoid unnecessary surgery. It is important to ensure there is no bowel blockage due to inflammation.

In addition, irritable bowel syndrome, Crohn's disease, ulcerative colitis share common features with FMF. Gastrointestinal manifestations in FMF can mimic all of these disorders. It is therefore important that patients with significant gastrointestinal problems work with a knowledgeable gastroenterologist to ensure that no additional problems arise.

Ethnicity

FMF was once considered a disease that only presented in certain populations. It was erroneously thought that only people of Mediterranean descent could be affected. Patients in any country can have the disease, regardless of their physical characteristics (i.e. blond hair, fair skin, etc). FMF presents equally both in men and women.

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Familial Mediterranean Fever & Autoinflammatory Diseases

FAMILIAL MEDITERRANEAN FEVER

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ENGLISH

Introduction

Familial Mediterranean Fever (FMF) is a genetic disease (monogenic congenital error in the MEFV gene) located on chromosome 16. This gene encodes a protein called "pyrin". Pyrin is a receptor found in the cell that normally controls the innate immune response (e.g. when detecting danger signals from the pathogen or the host). The mutation can lead to recurring activation of the pyrin inflammasome.

FMF can affect individuals of any ethnic group, but it is more prevalent in Mediterranean populations (despite where patients may reside) including individuals of Armenian, Turkish, Arabic, Sephardic and Ashkenazi Jews, Greek, Italian, and Spanish descent. FMF patients are found all over the world including: USA, Melungeons (southern Appalachia), Canada, Germany, Belgium, France, Netherlands, UK, Sweden, Argentina, Brazil, Georgia, Russia, Australia, Eastern European countries, Japan, China, etc.

There are many myths (medical inconsistencies) with regards to how patients present with this disease. It is typically described in the medical literature that FMF episodes are self-resolving and patients are healthy and fully functional between flares. However, this is contradictory to what patients report. While there are a few patients who may have full control of all of their symptoms, this is not the case for the majority.

Livneh diagnostic criteria

The requirements for diagnosis of FMF are based on the presence of 1 major or 2 minor criteria, or 1 minor plus 5 supportive criteria.

Major criteria:

- Peritonitis (generalized)
- Pleurisy (unilateral) or pericarditis
- Monoarthritis (hip, knee or ankle)
- Isolated fever

Minor criteria:

Incomplete attacks affecting one or more sites:

- Abdomen
- Lungs
- Joints
- Exertion-related leg pain
- Response to colchicine

Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, Migdal A, Padeh S, Pras M. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum. 1997 Oct;40(10):1879-85. *doi: 10.1002/art.1780401023. PMID: 9336425.*

Age of onset

FMF episodes usually begin before the age of 20 in approximately 90% of patients, and in more than half, the disease presents before the age of 10. There are also cases where patients have onset of FMF disease in early and even late adulthood. Disease manifestations may differ symptomatically during childhood versus adulthood.

Symptoms

The most common symptoms, which usually occur during flares, include: fevers, joint pain, and severe abdominal pain (in 95% of patients). Fever is a common symptom in children but does not always occur in adult patients.

The inflammation in FMF targets the serous membranes lining the body cavities, joints and surrounding the major organs. Inflammatory episodes may involve many membrane locations during a flare, resulting in pleuritis (thoracic pain), pericarditis (pain around the heart), synovitis (joint pain) and peritonitis (abdominal pain).

Other symptoms include painful headaches, skin rashes (erysipelas-like, psoriasis-like, eczema), diarrhea/constipation, vomiting, dizziness, fainting, fatigue, elevated heart rate/high blood pressure, hot flushes/sweating/chills and breathing difficulties.

Articular/joint involvement is a common and significant feature of FMF and is typically monoarticular (1 joint) or oligoarticular (4 or less joints) with likely affected joints being ankles, knees, hips, wrists, and elbows. Spondylitis (inflammation of one or more vertebrae) may present as one of the musculoskeletal symptoms of FMF.

Common symptoms include:

- high fever (more prevalent in childhood)
- severe stomach pain, bloating and cramping
- diarrhea/constipation
- joint pain/swelling
- pharyngitis
- leg pain/swelling/oedema
- rash (typically presents on the ankles)
- headache/dizziness
- fatigue
- mood swings/irritability
- brain fog/lack of concentration/memory problems

Less common symptoms include:

- severe chest pain
- testicular pain in males
- sterile meningitis

Diagnosing FMF

In most countries, diagnosis is made by rheumatologists or immunologists. Clinically diagnosing FMF includes the following:

A physical exam should be conducted to investigate all relevant symptoms. FMF&AID recommends that patients keep both a photographic and calendar diary detailing fevers and physical manifestations to share with the treating physician, which will aid with the diagnosis.

Reviewing the family medical history is imperative as other members may have like symptoms or fever patterns. This can be important for determining risk factors for MEFV inheritance, as the condition may be passed from parents to children.

Lab work should be done during a flare/attack and also in between, and repeated to possibly capture elevation of acute phase reactants (APR)/inflammatory markers, CRP, ESR, and SAA (not available in all countries). Additionally, proteinuria urinary levels (protein excretion abnormality), CBC, liver enzymes, calprotectin, ferritin/storage percent, cytokines, and immunoglobulins should all be ordered to provide a broad picture of a patient's innate inflammatory status. This comprehensive set of labs is also important as some patients may NOT present with elevated CRP, ESR or SAA during a flare. It is important to note that inflammation in FMF likely has undiscovered biomarkers.

Genetic testing, if available, is recommended to confirm the clinical diagnosis and to provide further analysis of possible genetic variants within the MEFV gene that causes FMF. The disease presentation may occur in patients with either homozygous or heterozygous mutations. Single mutated carriers may be as affected as those who are homozygous, and both types require treatment. Additionally, genetic testing via WES/WGS or targeted panel (i.e. Invitae) may confirm presence of another autoinflammatory disease.

It is not uncommon for patients to present with clinical symptoms, who carry certain MEFV variants, that have conflicting pathogenicity status. Mutations include E148Q, R202Q, A744S, P369S, I591T, and K695R.

To confirm diagnosis in these particular patients, it is essential that physicians request and review the benign variant report. Should both, the primary genetic and benign variant reports be negative (no mutations found), yet symptoms persist, the patient still requires treatment and should be diagnosed as uSAID (undifferentiated Systemic Autoinflammatory Disease).

Colchicine treatment (FMF&AID Colchicine brochure available)

The treatment for FMF is the ancient drug colchicine, which helps to control inflammation and offers protection from developing nephrotic syndrome and amyloidosis. Colchicine is safe for both children and adults, as well as pregnant and breastfeeding women.

Children's starting dose for colchicine, if the tablet comes as:

0.5mg (divide the tablet in half)	0.25mg
0.6mg (divide the tablet in half)	0.3mg
1mg (divide the tablet in 4 equal parts)	0.25mg

Adults' starting dose for colchicine, if the tablet comes as:

0.5mg	whole pill (or split as needed)
0.6mg	whole pill (or split as needed)
1mg (divide in half)	0.5mg

Colchicine toxicity is uncommon but can occur on its own or when combined with other contraindicated medications. The medications to avoid while on colchicine include: clarithromycin, erythromycin, antifungals and several others (for more detailed information, please see the FMF&AID Colchicine brochure). Please avoid all forms of grapefruit while on colchicine. Once a patient's appropriate dose has been established for symptom control, it should NOT be reduced nor stopped.

As per the EULAR recommendations for the management of FMF, (https://ard.bmj.com/content/75/4/644), colchicine may be increased up to a daily dose of 2 mg in children and 3 mg in adults, or the maximum tolerated dose. However, optimal dosing depends upon tolerance (especially GI), symptom control and liver enzyme impact. It is important for patients to find the most appropriate individualized dose to alleviate symptoms. It is recommended that colchicine should be started at the lowest dose of 0.5mg/0.6mg (tablets can be split further, if necessary), to allow for acclimation to the drug. Since colchicine is known to cause GI issues including stomach pain/cramps and diarrhea, it should be increased gradually. Allowing for an adjustment period while dosing up slowly, will ensure for the most appropriate response. Physicians should anticipate follow-up appointments with new colchicine users to monitor CBC/ white cells and liver enzymes and to ensure that patients are having a safe and effective response to the medication.

Patients can be intolerant or resistant to colchicine. Intolerant means that even at the lowest possible dose, the patient will have severe side effects.

Resistant means no amount of colchicine will be effective. In these cases, biologic treatment must be considered. Patients who do well on colchicine, but do not have enough symptom control, will require an additional biological medication added to their treatment protocol. Please note that each IL-1 inhibitor does not work in the same way. Should patients fail one, another one should be trialed.

Despite adding a biologic, it is advisable to continue on colchicine. However, some patients may be instructed to lower their colchicine dose. For patients who are intolerant to colchicine, biologic medications should be made available as soon as possible.

Biologic treatment

The first line of biologics recommended for FMF patients are interleukin-1 inhibitors (IL-1): Kineret (anakinra), Ilaris (canakinumab) and Arcalyst (rilonacept – USA only). Patients not responding to Kineret (IL-1α) should be offered Ilaris (IL-1β), and vice versa, as each medication works differently. Additionally, patients who fail IL-1 treatments may have a better response to the IL-6 inhibitor Actemra (tocilizumab). All patients on biologics must be monitored and treated for infections, skin reactions, and lung problems.

Ilaris recommendations:
Children weighing less than 40kg are dosed by body weight with a recommended dose of 2mg/kg every 4 weeks by subcutaneous injection. Dosing can be increased to 4mg/kg every 4 weeks in patients not having an adequate response. Children weighing 40kg or more should be given 150mg every 4 weeks.
Adult patients weighing 40kg or more should be given 150mg every 4 weeks by subcutaneous injection. Dosing can be increased to 300mg every 4 weeks in patients not having an adequate response. Source: https://www.ilarishcp.com/assets/pdfs/ilaris_dosing_guide.pdf

Kineret recommendations:
Children weighing less than 50kg are dosed by body weight with a recommended dose of 1-2 mg/kg/day by subcutaneous injection. Patients weighing 50kg or more are dosed with 100mg/day. In children with inadequate response the dose can be escalated up to 4 mg/kg/day. The efficacy data of Kineret in children under 2 years of age with FMF are limited.
Adult patients weighing 50kg or more should be given 100mg/day by subcutaneous injection. Source: https://www.ema.europa.eu/en/documents/product-information/kineret-epar-product-information_en.pdf

Rare side effects of biologics

Apart from the side effects listed below, patients using these medications may also experience weight gain (despite no dietary changes), swollen lymph nodes, fluid retention, post-nasal drip, synovitis, lung problems, etc.

Source: https://www.kineretrx.com/
The most common side effects of KINERET include: Injection site skin reactions, including redness, swelling, bruising, itching, and stinging. Most injection site reactions are mild, happen early during treatment, and last about 14 to 28 days. Kineret may also cause: headaches, nausea, vomiting, diarrhea, joint pain, fever, flu-like symptoms, sore throat or runny nose, sinus infection, abdominal pain.

Source: https://www.ilaris.com/important-safety-information
The most common side effects of ILARIS when used for the treatment of FMF: cold symptoms, upper respiratory tract infection, runny nose, sore throat, nausea, vomiting, diarrhea (gastroenteritis), and injection site reactions (such as redness, swelling, warmth, or itching).

Emergency kit

All FMF patients, in particular those on biologics, are more susceptible to getting infections, fungal issues, breakthrough flares and other immunological problems due to high levels of innate inflammation. It is therefore recommended that patients be provided with emergency medications prior to going on any biologic medication to be proactively prepared. The emergency kit should contain steroids, antibiotics, antihistamines, and pain medications. Patients should be instructed how to use all medications to control any unforeseen complications in an effort to avoid unnecessary use of emergency services. Patients should always follow up with their treating physician, when requiring use of these medications.

Photo by Vitalii Petrushenko on Unsplash

Post-treatment monitoring

It is recommended by EULAR (European League Against Rheumatism) for patients to have a follow up every 6 months to evaluate treatment efficacy, flare breakthroughs, and to monitor acute-phase reactants (APR). Laboratory tests are recommended to monitor liver enzymes, complete blood count, kidney function, creatinine phosphokinase (CPK) and to identify proteinuria. The preferred APR are CRP, ESR and SAA. There are many FMF cases where patients rarely present with elevated inflammatory markers (CRP, ESR, WBC) in or out of flaring. This may be due to other inflammatory presentation (cytokines) that are not typically tested.

Photo by Vitalii Petrushenko on Unsplash

Overlapping diseases and comorbidities

One of the most common comorbid diseases presenting with FMF is Behcet's. This disease combination is commonly seen in patients of Turkish origin, but it is not limited to this ethnic group. FMF-Behcet's patients often present with multiple mouth and genital ulcers, body sores, eye issues, GI problems, and vasculitis. Both of these diseases presenting together often will alter the presentation of the patient's symptoms. This is likely due to the mutated MEFV gene effect.

Other FMF comorbidities noted in the literature include: Crohn's disease, Irritable Bowel syndrome, Hashimoto's, anaemia, psoriasis, asthma, uveitis, epilepsy, Sjogren's syndrome, Ankylosing spondylitis, von Willebrand disease, Ehlers Danlos syndrome, amyloidosis, Hyperactivity disorder (ADHD)/autism, Juvenile Idiopathic Arthritis, Henoch-Schönlein purpura, Raynaud's, fatty liver disease (NAFLD), fibromyalgia, etc.

Social impact

Familial Mediterranean Fever limits the daily activities of both children and adult patients in many areas including school and work, personal relationships, and social activities. Attendance and performance are both impacted due to the unpredictability of symptoms and flares, which can add stress affecting the patient's physical and emotional well-being. Sleep quality is a common issue for FMF patients and they should be evaluated for comorbid sleep apnea. Other issues include anxiety, depression, fatigue, and impaired concentration/brain fog.

Documenting symptoms

Patients should keep a symptom diary with detailed notes on all organs/body parts impacted before, during, and after flare. This type of documentation can be very helpful to track and present how the disease manifests in a particular case. Recording fevers (AM/PM), GI distress, bone pain, fatigue status/activity, rashes, pain rating, all per specific body part can help the clinician have a clear overview of the symptoms occurring during a flare. Keeping this diary over time will also allow patients to spot trends and ask additional pointed questions. Another way to help develop a disease diary is by taking pictures of rashes, joint swelling, and any other visible symptom.

Triggers

Triggers that may provoke a flare include: physical activity, positive & negative stress, environmental temperatures, illness/infection, accidents/trauma, lack of sleep, fatigue, menstruation, gluten, dairy or other food intake, sitting or standing for long periods of time (travel, employment, school), but often, the triggering factors remain unknown.

Photo by sporlab on Unsplash

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