Familial Mediterranean fever

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Familial Mediterranean fever

1 Familial Mediterranean fever (FMF) is an autoinflammatory genetic disorder that mainly affects people of Mediterranean origin.

2 ❖ FMF is characterized by recurrent episodes of fever and serositis (chest, abdomen, joints), leading to painful attacks early during childhood.

3 ❖ The onset of symptoms usually presents during childhood, especially before the age of 20.

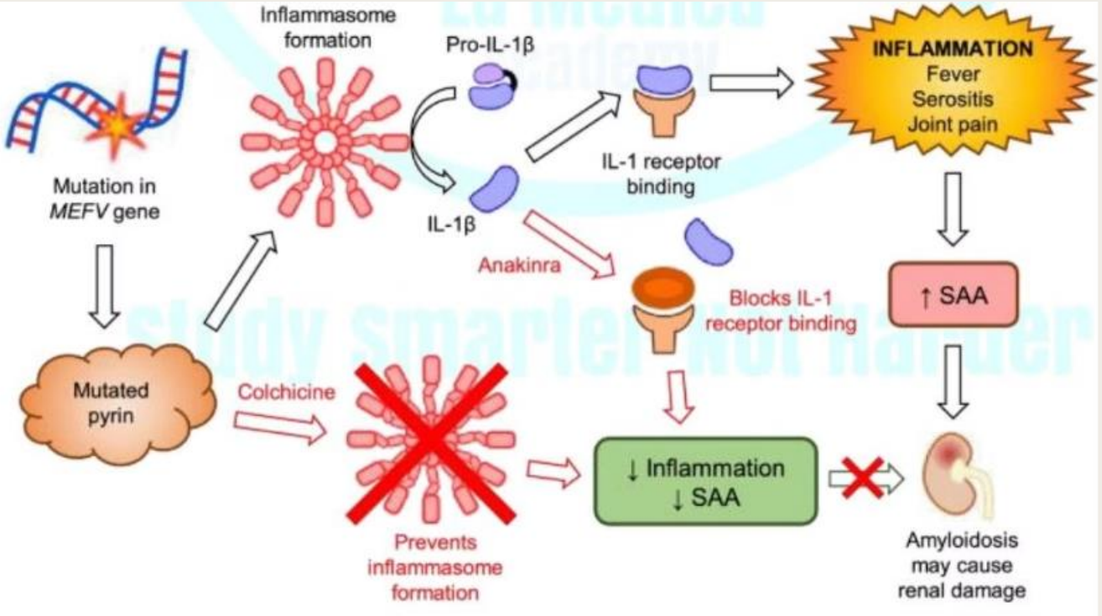
4 ❖ Most episodes gradually develop over the course of two to four hours and usually resolve spontaneously between six hours to four days after onset.

5 ❖ Patients do not experience any symptoms between attacks.

6 ❖ Nonetheless, treatment is necessary as it helps prevent recurrent episodes and severe secondary complications that may be fatal.

7 ❖ Amyloidosis is the most fatal complication of FMF which can cause kidney failure.

Etiology



o FMF is a genetic disorder that is inherited in an autosomal recessive manner. The responsible gene for FMF is the MEFV gene, located in the short arm of chromosome

16. o The MEFV gene encodes a protein called pyrin, which consists of 781 amino acids. 300 different mutations of this gene have been identified as potential causes of FMF.

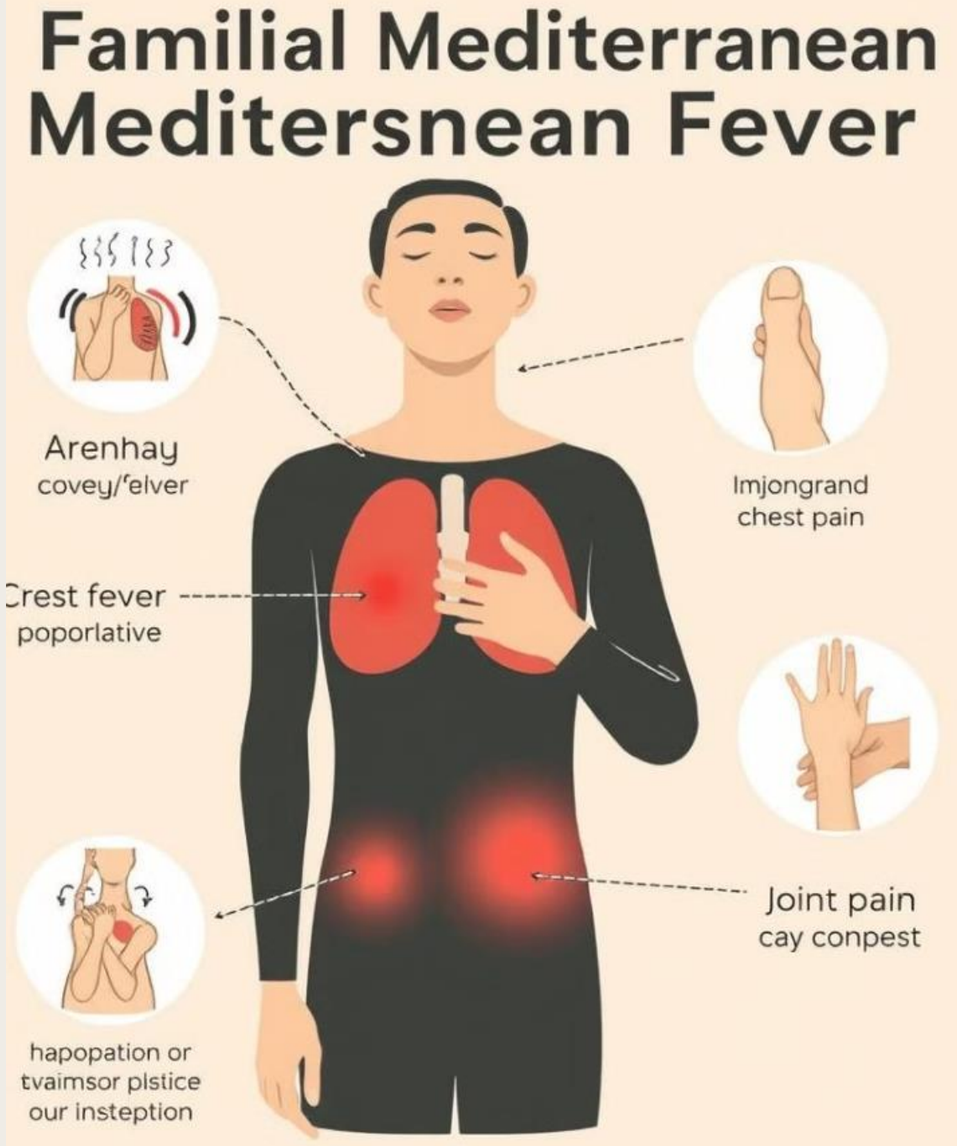
Clinical features

1 Familial Mediterranean fever usually presents with periodic fevers and severe chest, abdominal, or joint pain associated with the serositis, followed by periods where individuals remain symptom-free.

2 Some individuals also experience symptoms prior to the episode, such as irritability, anxiety, nausea, skin irritations, scrotal swelling, or even myalgias.

3 For some, there are specific triggering factors that may cause an attack, such as severe stress, cold exposure, excessive exercise, recent infection or surgery, and even menstruation.

4 With time, as patients age, the frequency decreases, and the severity of attacks becomes less intense.



Fever and Abdominal Pain in FMF

1

1. Fever

In an FMF crisis, especially in younger ages, fever is the most common symptom and may even be the only symptom present.

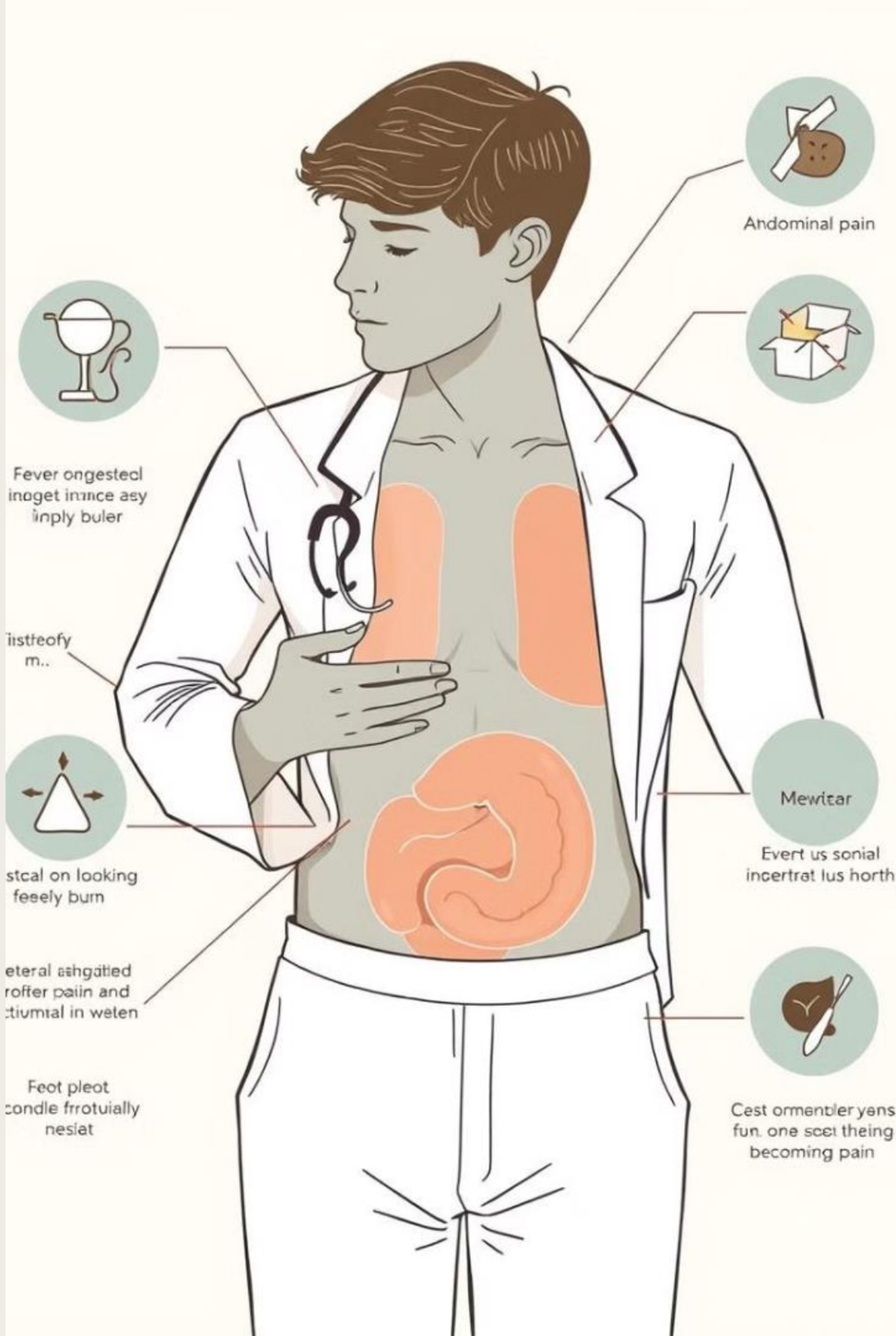
- The individual's temperature may vary from low-grade fever up 40°C.
- The fever may not be present during the episode if the individual has already begun the appropriate treatment with colchicine.

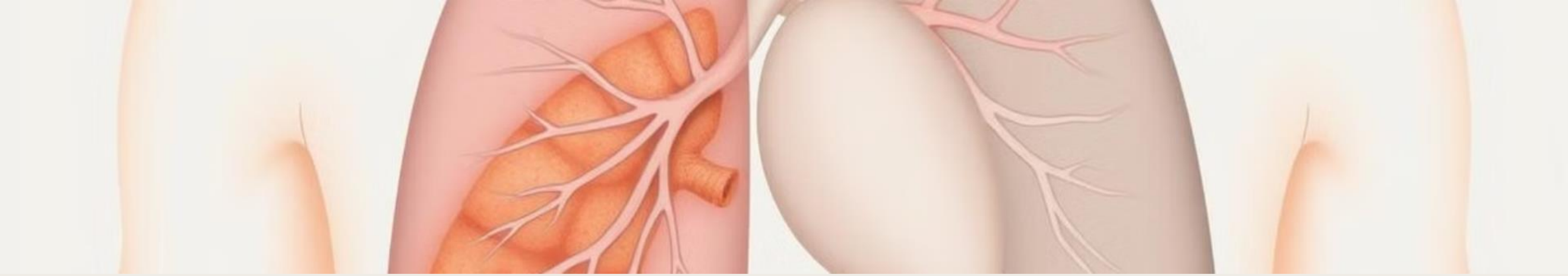
2

2. Abdominal pain

An abdominal pain attack is the most common type of attack in FMF.

- Abdominal pain could be localized initially and then become generalized.
- On physical examination, abdominal distension, guarding, rebound tenderness, and decreased bowel sounds are appreciated due to peritonitis.
- The episode spontaneously resolves in 2 to 3 days.





Chest Pain in FMF

3. Chest pain

Chest pain, which is typically unilateral, can develop as a result of the inflammation of the pleura and may worsen when breathing deeply or coughing (i.e., pleuritic chest pain).

Along with pleuritic pain, pericarditis can occasionally be present as retrosternal chest pain.

Pleural and pericardial friction rubs can be audible during auscultation.

Although pleural effusion can also develop, it is mostly a mild effusion and seldom is large enough to appreciate decreased breath sounds on examination.

Joint Pain in FMF

4. Joint pain

Large joints in the lower extremities, such as the hip, knee, or ankle joints are most commonly affected in an FMF episode.

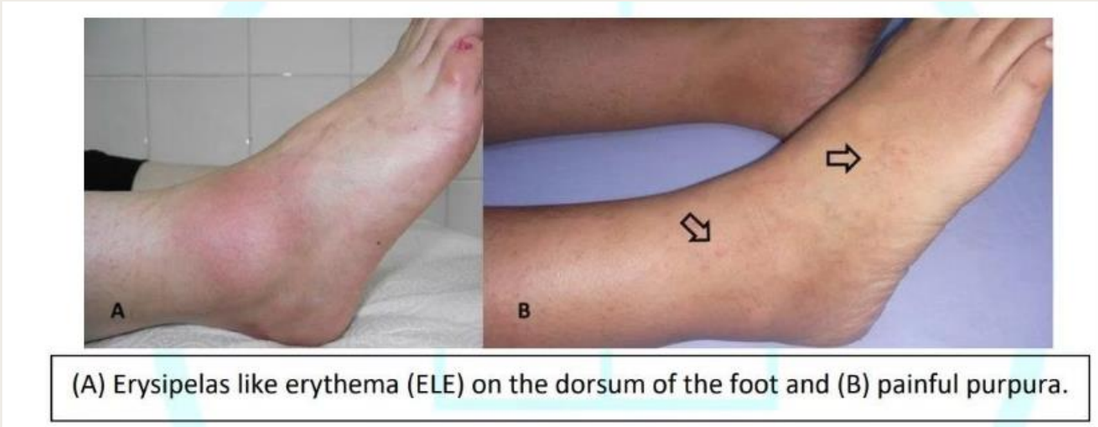
The affected individuals frequently complain of intense pain in one joint. Rarely, multiple joints are simultaneously affected.

Physical examination may reveal a restricted range of motion of the affected joint. Redness and swelling are less frequent. While complete recovery from an episode is typical, chronic arthritis can occasionally develop.

Skin Lesions in FMF

5. Skin lesions

o Skin lesions that are red, raised, with distinct margins resembling erysipelas are most commonly identified on the lower extremities (e.g., leg, ankle, or foot) and they tend to resolve spontaneously. o Physical examination may reveal red, raised lesions that are tender to the touch. Red or purple-colored spots or patches, like purpura, can be also seen on the face, limbs, and trunk of the affected individuals. o This is more common in Jews but less common in Arabs.



(A) Erysipelas like erythema (ELE) on the dorsum of the foot and (B) painful purpura.

Other Symptoms in FMF

- **6. Scrotal swelling**

  - This presents as a unilateral scrotal swelling, which is tender to palpation on the exam.

  - This is caused by transient inflammation of tunica vaginalis and resolves within 24 hours.

- **7. Myalgia**

  Myalgia is non-specific and could involve upper or lower extremities.

  Muscle tenderness is observed on physical examination.

  Prolonged febrile myalgia is very rare.

Diagnosis

1 - FMF is generally a clinical diagnosis.

2 - The classic presentation of symptoms supported by the presence of family history and response to colchicine help confirm a diagnosis.

3 - Laboratory and radiographic studies may help support the diagnosis or exclude other causes.

Laboratory analysis: Familial Mediterranean Fever

Laboratory analysis can reveal elevated WBC count with neutrophil predominance.

- Elevation of the acute phase reactants such as fibrinogen, erythrocyte sedimentation rate, serum amyloid A (SAA) protein, and C-reactive protein, although commonly found, are nonspecific.
- They can be monitored while the patient is on treatment to document the response to the therapy.
- Electrocardiogram may reveal diffuse ST-segment elevation in the case of pericarditis.
- The synovial fluid analysis shows sterile fluid with elevated nucleated while cells.
- A computed tomography scan of the abdomen is commonly performed to exclude other causes of abdominal pain, including an acute abdomen.

Genetic Testing and Diagnostic Criteria

Genetic Testing

-

Genetic testing can help confirm the diagnosis in cases with atypical presentation of FMF. However, around 10 % of patients who meet diagnostic criteria based on the clinical presentation do not have any mutation.

Diagnostic Criteria

In order to facilitate the diagnosis of FMF the Tel-Hashomer diagnostic criteria have been established.

They have been proven very accurate, having a sensitivity and specificity of more than 95% and 97%, respectively. To confirm the diagnosis in suspected cases, two or more major criteria or one major plus two minor criteria are required.

For the criteria, typical attacks consist of fever (rectal - 38°C), pain due to inflammation , three or more recurrences of the attacks, and duration of 12 to 72 hours.

Major and Minor Criteria for FMF Diagnosis

Major Criteria

Typical attack with one or more of the following symptoms:

- Abdominal pain
- Joint pain (e.g., hip, knee, ankle)
- Chest pain (e.g., unilateral pleuritis or pericarditis)
- Scrotal swelling
- Skin manifestations
- Muscle pain
- Fever alone (usually recurrent attacks with fever only and no other identifiable cause)

Minor Criteria

Incomplete attack including one or more of the following symptoms:

- Abdominal pain
- Joint pain
- Chest pain
- Leg pain on exertion
- Positive response to colchicine
- Nephropathic amyloidosis

Supportive Criteria for FMF Diagnosis

1 Family and Ethnic Factors

- Family history of FMF
- Vulnerable ethnic origin
- Early age at onset (under 20)
- Consanguinity of parents

2 Attack Characteristics

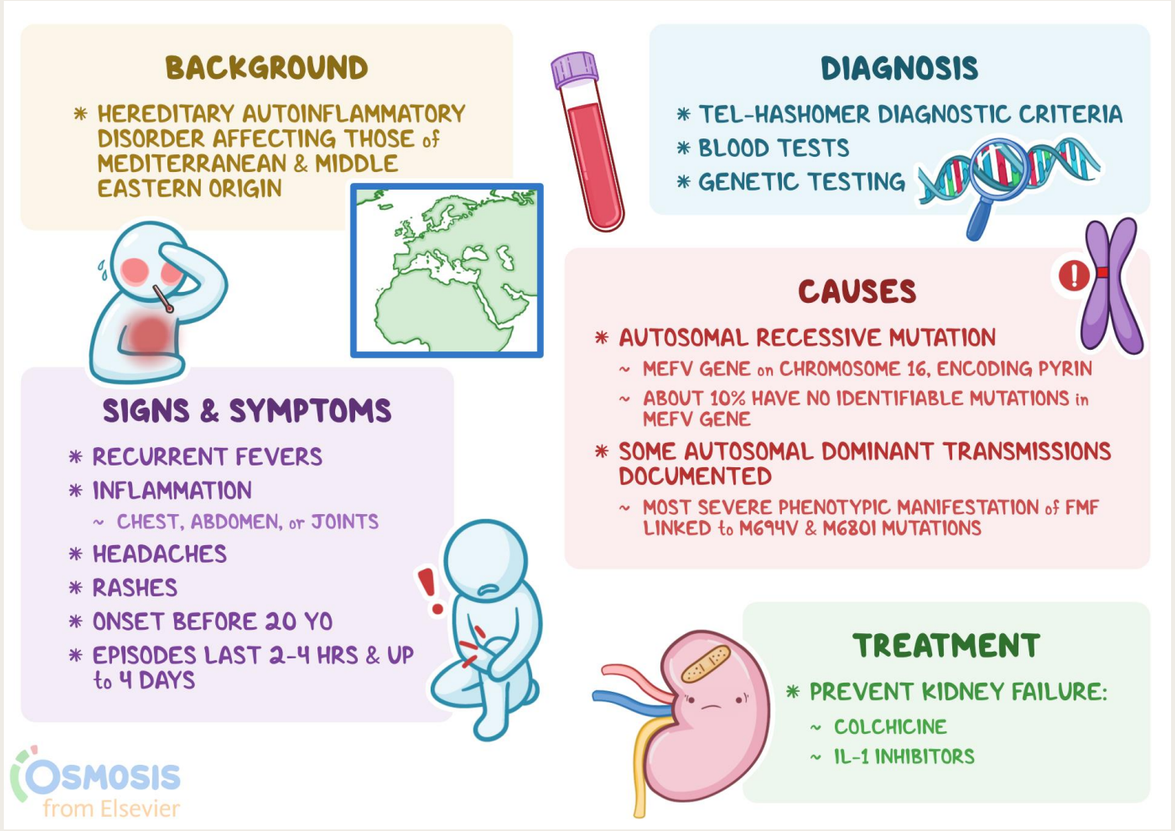
- Attacks with spontaneous resolution
- No symptoms between the attacks
- Severe attacks requiring bed rest

3 Medical Findings

- Presence of elevated white cell count or elevated acute phase reactants in the blood
- History of laparotomy or appendectomy with no pathology
- Episodic proteinuria or hematuria

Familial Mediterranean Fever Illustration

This image illustrates key aspects of Familial Mediterranean Fever, providing a visual representation of the condition and its effects on the body.



Complications of Familial Mediterranean Fever

Abnormal protein in the blood

During attacks of familial Mediterranean fever, your body may produce an abnormal protein (amyloid A). The protein can accumulate in body and cause organ damage (amyloidosis).

Kidney damage

Amyloidosis can damage the kidneys, causing nephrotic syndrome. Nephrotic syndrome occurs when your kidneys' filtering systems (glomeruli) are damaged. People with this condition may lose large amounts of protein in their urine. Nephrotic syndrome can lead to blood clots in your kidneys (renal vein thrombosis) or kidney failure.

Infertility in women

Inflammation caused by familial Mediterranean fever may also affect the female reproductive organs, causing infertility.

Joint pain

Arthritis is common in people with familial Mediterranean fever. The most commonly affected joints are the knees, ankles, hips and elbows.

First-line Treatment for FMF

1

Colchicine

The first-line treatment established for FMF is Colchicine.

2

Mechanism

Which is a medication used to suppress neutrophil chemotaxis (i.e., directed migration of neutrophils towards inflammatory tissues) and prevent the inflammatory events seen in FMF.

3

Administration

Therefore, lifelong administration of this medication is typically suggested.

4

Side Effects

The most common side effects of the treatment are diarrhea and vomiting. These side effects are dose-dependent and more common at higher doses. Other uncommon side effects are myelosuppression, hepatotoxicity, nephrotoxicity, myopathy, neuropathy, and hypersensitivity reaction.

5

Safety

Colchicine is considered safe during pregnancy and breastfeeding.

Second-line and Alternative Treatments for FMF

1

IL-1 Inhibitors

The second-line treatment for patients with FMF resistant to colchicine or who are intolerant to colchicine is an IL-1 inhibitor, such as anakinra or canakinumab.

The effectiveness of IL-1 inhibitors in preventing FMF amyloidosis is not completely established.

2

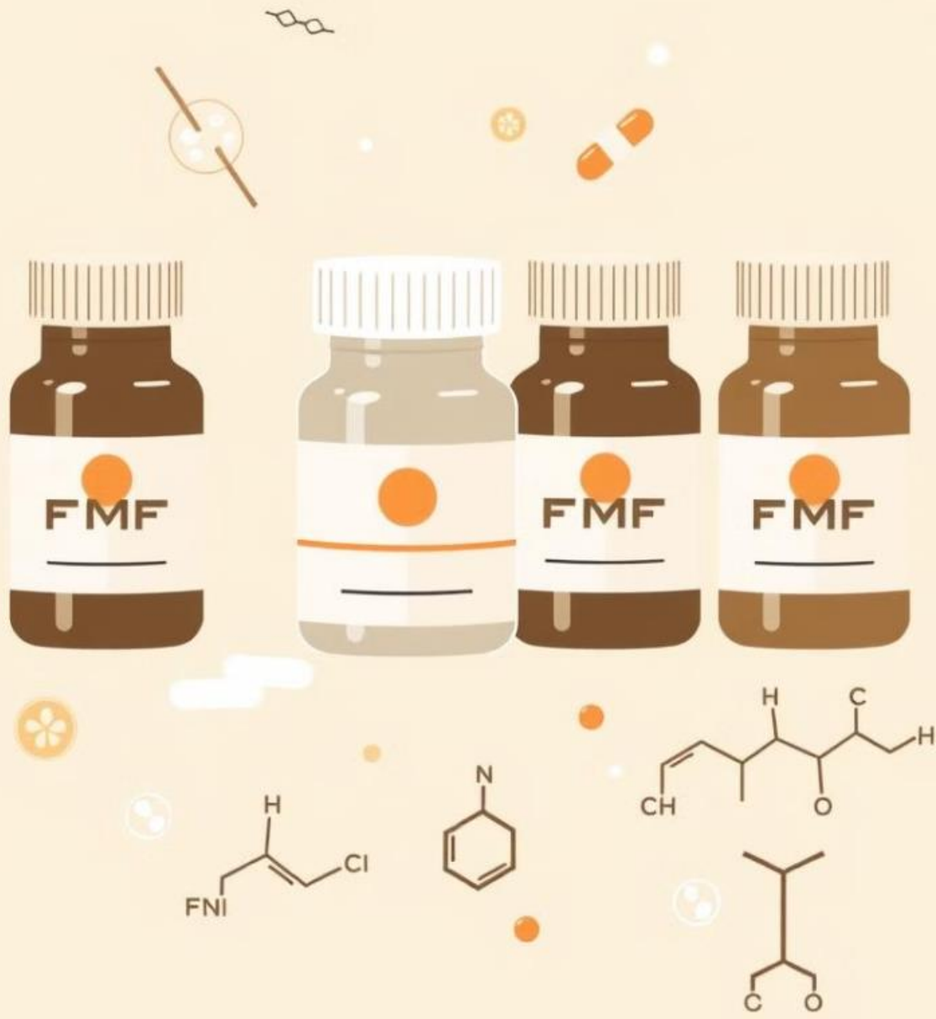
TNF-alpha Inhibitors

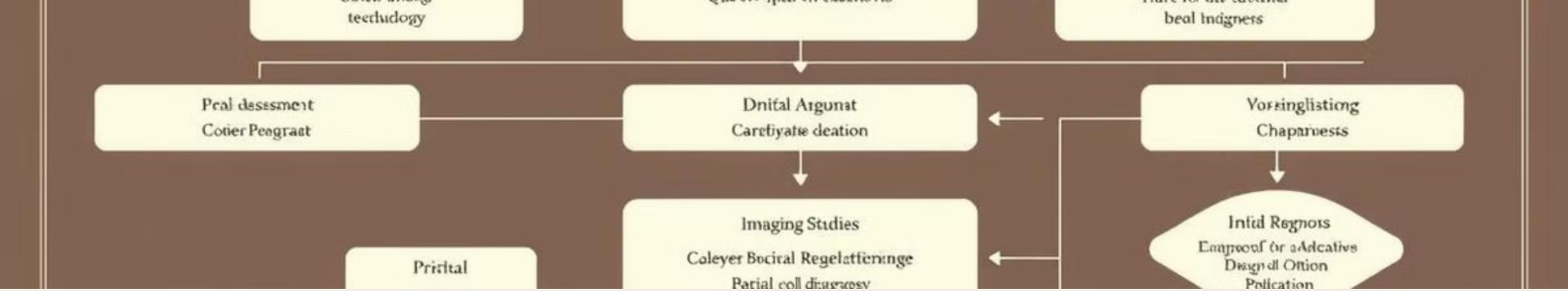
Tumor necrosis factor (TNF)-alpha inhibitors (e.g. thalidomide, infliximab, and etanercept) have also been recommended in some cases; however, their efficacy is still not well established.

3

Selective Serotonin Reuptake Inhibitors

Lastly, selective serotonin reuptake inhibitors (e.g., escitalopram, paroxetine) can also minimize the frequency of episodes in FMF, suggesting that depression and stress may also play a significant role in FMF morbidity.





Differential Diagnosis for FMF

Many diseases can mimic the signs and symptoms associated with FMF. Therefore, a detailed history and physical examination of patients, including the history of attacks, history of fever, and family history, can help differentiate other diagnoses from FMF.

1 Acute Conditions

- Acute abdomen
- Periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA)

2 Autoimmune Conditions

- Juvenile idiopathic arthritis
- Systemic lupus erythematosus (SLE)
- Rheumatoid arthritis (RA)

3 Genetic Conditions

- Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS)

Thank You

This concludes the presentation on Familial Mediterranean Fever. Thank you for your attention.