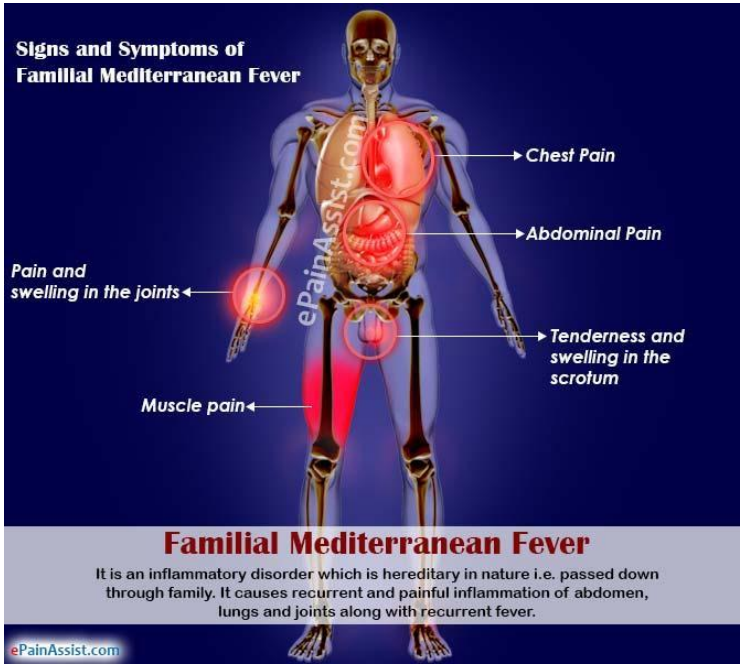

FMF

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Introduction

- Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disorder characterized by recurrent bouts of fever and serosal inflammation
- Autoinflammatory diseases:
  - TNF-R-associated periodic syndrome (TRAPS) (55-kd TNFRSF1A gene mutation: C70R, P46L)
  - Hyper IgD periodic fever syndrome (HIDS) (MVK gene mutation--> mevalonate kinase deficiency)
  - Familial cold urticaria (FCU)

Introduction

- Autosomal recessive inherited periodic disease
- Sephardic, North African Jews, Armenians, Arabs, Druze and Turks are affected
- Characterized by sporadic, unpredictable attacks of fever and serosal inflammation
- Most patients with FMF experience their first attack in early childhood.
- The initial attack occurs before the ages of 10-20y

Pathogenesis

- Mutated MEFV gene
- The *MEFV* gene encodes pyrin, a 781 amino acid protein that is expressed predominantly in the cytoplasm in cells of myeloid lineage (among circulating cells), synovial fibroblasts
- Pyrin acts as an intranuclear regulator of transcription of the peptides involved in inflammation

Clinical presentation

- Recurrent episodes of fever and severe pain (due to serositis at one or more sites
- The onset of pain and fever is usually abrupt, peaking soon after onset.
- Episodes last for one to three days and then resolve spontaneously.
- The frequency of attacks is highly variable, even in a given patient, and it is unusual for a patient to describe a consistent triggering event.
- **Abdominal pain** — 95% of patients have episodic abdominal pain
- Abdominal pain and tenderness may initially be localized and then progress to become more generalized.
- Guarding, rebound tenderness, rigidity, and an adynamic ileus are often present.
- **Chest pain** — 45%.
- Chest pain may be due to inflammation of the pleura or referred pain from subdiaphragmatic inflammation

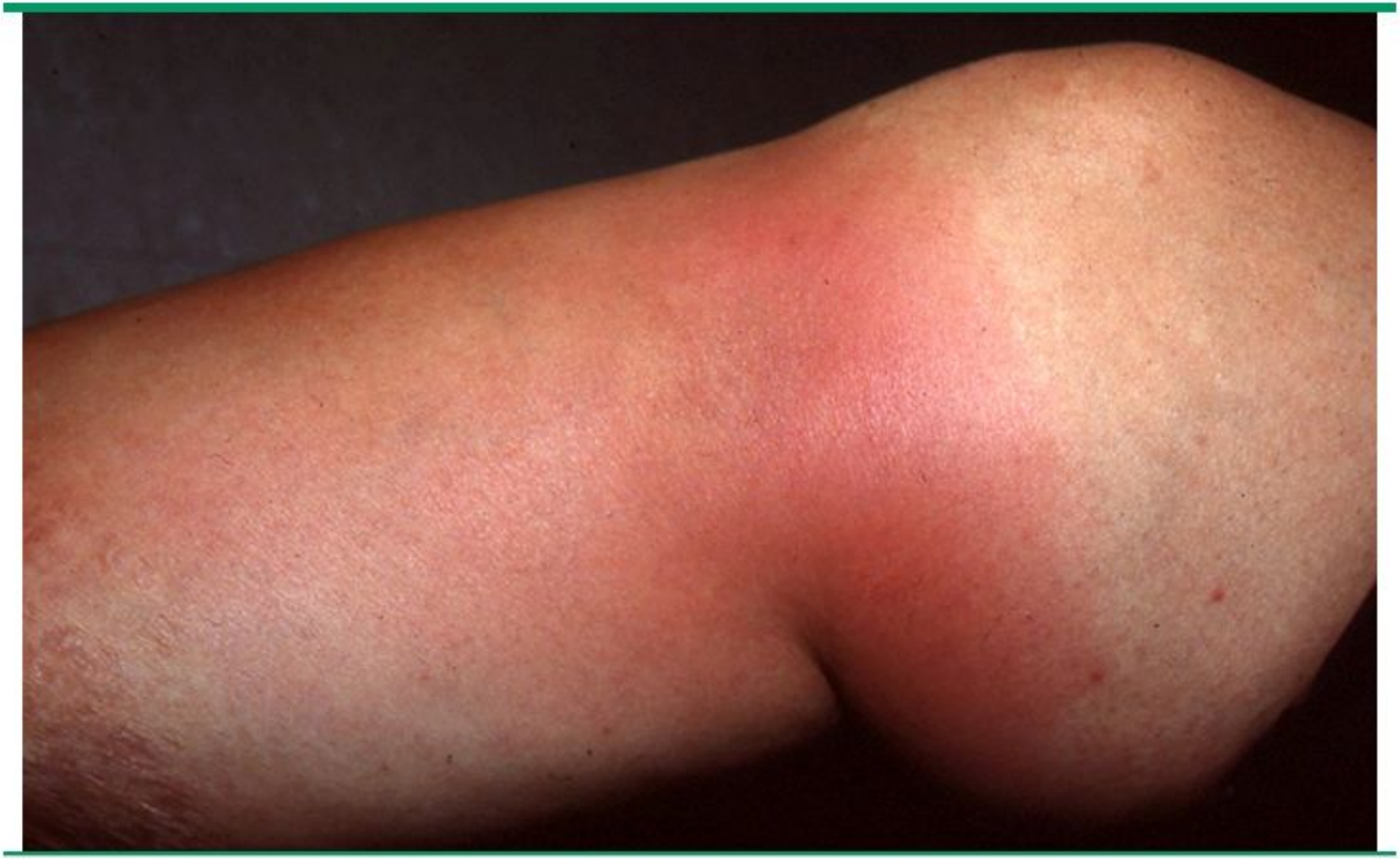
Clinical presentaion

- **Joint pain** — 75 % suffer from sudden attacks of articular pain, which may be precipitated by minor trauma or effort such as prolonged walking.
- Monoarticular or oligoarticular and involve one of the large joints (knee, ankle, hip)
- Gradual resolution of the signs and symptoms occur after peaking in 24 to 48 hours. The synovial fluid analysis is typically sterile, with a nucleated white cell count ranging from 200 to >100,000
- The synovitis usually resolves completely without joint destruction.
- However, severely protracted cases can result in permanent deformity, functional limitation, osteoporosis, and aseptic necrosis.

Clinical Presentation

- **Erysipelas-like skin lesion** — The lesion is typically 10 to 35 cm^2 in area, tender, raised, and erythematous
- Occurs on the lower leg, ankle, or foot
- Erysipelas-like skin lesions may be the presenting feature of FMF in children and may be misdiagnosed as an infectious erysipelas or cellulitis
- Children with myalgia and erysipelas-like skin lesions during attacks are at increased risk for subclinical inflammation during attack-free intervals, as evidenced by elevation of acute phase

Familial Mediterranean fever



Clinical presentstion

- **Acute pericarditis** – small pericardial effusion detected incidentally
  - Clinical features of pericarditis include chest pain (sharp and pleuritic, improved by sitting up and leaning forward), pericardial friction rub, and widespread ST segment elevation on ECG
- **Acute orchitis** – Acute scrotal swelling and tenderness due to orchitis is rare
- **Febrile myalgia** – protracted bouts of febrile myalgia, up to six weeks. Usually involves the lower extremities but, in some cases, may be more . CPK is normal. Although the etiology is not clear, febrile myalgias may be due to an underlying vasculitis.
- ●**Aseptic meningitis** – rare

Laboratory findings

- Acute attacks are accompanied by elevation of serum markers of systemic inflammation
  - Leukocytosis
  - Neutrophilia
  - ESR, CRP,
- The presence of otherwise unexplained proteinuria in between attacks is suggestive of renal amyloidosis

Diagnosis

- ≥1 major criteria
- ≥2 minor criteria
- 1 minor plus 5 supportive criteria
- 1 minor criterion plus ≥ 4 of the first five supportive criteria
- Typical attacks are defined as recurrent (≥3 of the same type), febrile (≥38°C) and short (lasting between 12 hours and 3 days)

Detailed criteria for the diagnosis of familial Mediterranean fever

Major criteria
Typical attacks
1. Peritonitis (generalized)
2. Pleuritis (unilateral) or pericarditis
3. Monoarthritis (hip, knee, ankle)
4. Fever alone
Minor criteria
1-3. **Incomplete** attacks involving one or more of the following sites:
1. Abdomen
2. Chest
3. Joint
4. Exertional leg pain
5. Favorable response to colchicine
Supportive criteria
1. Family history of FMF
2. Appropriate ethnic origin
3. Age <20 years at disease onset
4-7. Features of attacks:
4. Severe, requiring bed rest
5. Spontaneous remission
6. Symptom-free interval
7. Transient inflammatory response, with one or more abnormal test result(s) for the white blood cell count, erythrocyte sedimentation rate, serum amyloid A, and/or fibronogen
8. Episodic proteinuria/hematuria
9. Negative laparotomy or removal of normal appendix
10. Consanguinity of parents

Genetic testing

- Used to support, but not exclude, the diagnosis of FMF
- FMF is usually inherited as an autosomal recessive trait
- Individuals who have two pathogenic mutations in the *MEFV* gene confirm the diagnosis
- 25% of patients who meet clinical criteria for FMF have only one identifiable mutation

Treatment

- The goals of therapy for familial Mediterranean fever (FMF) are to prevent acute attacks and minimize subclinical inflammation in between attacks, and to prevent the development and progression of amyloidosis
- Initial treatment with colchicine is indicated
- At doses of 1 to 2 mg/day, colchicine is safe even when given continually over decades
- Side effects, most commonly gastrointestinal (eg, diarrhea, nausea, vomiting), are uncommon at low doses (0.5 to 1.2 mg per day). Less common (<1 percent) side effects include bone marrow suppression, hepatotoxicity, and myotoxicity. Chronic renal insufficiency or liver cirrhosis leading to increased colchicine levels is a major risk factor for side effects.
- Approximately 5 to 10 % of FMF patients are colchicine-resistant
- Interleukin (IL)-1 inhibition is the preferred second-line therapy for these patients It is unknown whether IL-1 inhibitors have a beneficial effect on amyloidosis
- Colchicine should be continued during pregnancy and breastfeeding

Complications

- Amyloid deposition can occur in the kidneys, spleen, liver, gastrointestinal tract and subsequently in the heart, thyroid, and testes
- Progressive secondary (AA) amyloidosis is a major cause of mortality
- Patients can present with renal amyloidosis as the first and only manifestation
- Patients with renal amyloidosis can present with asymptomatic proteinuria or clinically apparent nephrotic syndrome and gradually develop progressive nephropathy with end-stage renal disease
- End-stage renal disease develops 2 to 13 years after the onset of proteinuria
- There is poor correlation between the severity or frequency of attacks of FMF and the extent of amyloidosis in individual patients
- The incidence of AA amyloidosis has markedly decreased with the use of colchicine

Complications

- **Small bowel obstruction** — Recurrent attacks of peritonitis may lead to adhesions and small bowel obstruction
- **Infertility** — Pelvic adhesions and ovulatory dysfunction can reduce fertility in female patients. In men, fertility may be decreased due to azoospermia from testicular amyloidosis