

# Familial Mediterranean Fever

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PGY-2

# Outline

- The Case
- Background
- Clinical Manifestations
- Genetics
- Pathophysiology
- Secondary Amyloidosis
- Management

# The Case

- AA: 31 F dx FMF age 22
- Typical symptoms since age 5
- Recurrent episodes of fever with abdominal pain, pleuritic chest pain, nausea/vomiting, joint swelling
- Strong family hx: mother, brother, sister
- Genetic studies: E148Q/M694I complex allele; E148Q allele

# Background

- Autosomal recessive inheritance
- Mediterranean and Middle Eastern ethnic groups: Serphadic Jews, Armenians, Turks, North Africans and Arabs
- Prevalence varies with populations:
  - Israel: 1 in 500 (carrier freq varies)
  - Lebanon: 1 in 500 (lower freq in US)

# Clinical Presentation

- Phenotype I: recurrent attacks of fever, serositis, erysipelas like rash, arthritis; asymptomatic in between
- Phenotype II: AA amyloidosis is primary presenting feature without history of typical attacks

# Clinical Presentation

- Initial attack usually in childhood, 90% before age 20, only 5% after age 30
- Frequency of attacks is variable
- No clear precipitants (? excessive exercise, stress, high fat diet, hormonal changes)
- Severity and frequency tends to decrease with age

# Major Clinical Manifestations

- Fever: duration 12h to 3d
- Peritonitis: Severe abdominal pain , may precede fever, resolves 1-2d after temp normal
  - Constipation/nausea/vomiting in adults, diarrhea common in children
  - Adhesions are rare
- Pleuritis: Chest pain with occasional transient effusions, duration 3-7d

# Clinical Manifestations: Synovitis

- Usually mono/oligoarthritis involving lower extremities
- Acute form:
  - peak 1-2 d resolves within 7 d
  - cloudy to purulent synovial fluid but sterile
  - usually complete resolution
  - mainly knees, ankles and wrists

# Clinical Manifestations: Synovitis

- Chronic form:
  - persists > 1 mo
  - damage/deformity can occur
  - mainly hips and knees, sacroiliitis is rare
- Rarely migratory polyarthritits
- Varies with ethnic groups (North Africans >> Armenians/Ashkenazi Jews)

# Other Clinical Manifestations

- Erysipelas like rash: sharply demarcated red, tender and swollen patches on lower extremities
  - Dermal hyperemia, PMN infiltration on biopsy
- Myalgias: arms and legs, may last for weeks after an attack
- Pericarditis: 0.5% of patients, tamponade/constrictive pericarditis is rare

# Other Clinical Manifestations

- Orchitis: scrotal edema and pain, self-limited
- Association with vasculitis: PAN, HSP
- Splenomegaly: negative for amyloid
- Aseptic meningitis is very rare
- No specific lab abnormalities: ESR, CRP, fibrinogen, SAA elevated during attacks

# Tel-Hashomer Diagnostic Criteria

- Major Criteria
  - Recurrent febrile episodes accompanied by peritonitis, synovitis or pleuritis
  - Amyloidosis of the AA type without predisposing disease
  - Favourable response to continuous colchicine treatment
- Minor criteria
  - Recurrent febrile episodes
  - Erysipelas-like erythema
  - FMF in a first degree relative
- Definitive diagnosis: 2 major or 1 major + 2 minor
- Probable diagnosis: 1 major + 1 minor

# Genetics

- FMF gene = MEFV, located on short arm of chromosome 16
- Encodes a 781 amino acid protein: pyrin/marenostrin
- Expressed exclusively in the cytoplasm of circulating granulocytes
- Exact function not well elucidated

# Genetics

- 3 main mutations found in 85% of carriers
- At least 23 mutations have been identified at this time, mainly in exon 10
- Genotype-Phenotype correlation exists
- V726A mutations associated with milder disease, lower incidence of amyloidosis
- E148Q mutation is mildest, least penetrant phenotype

# Genetics

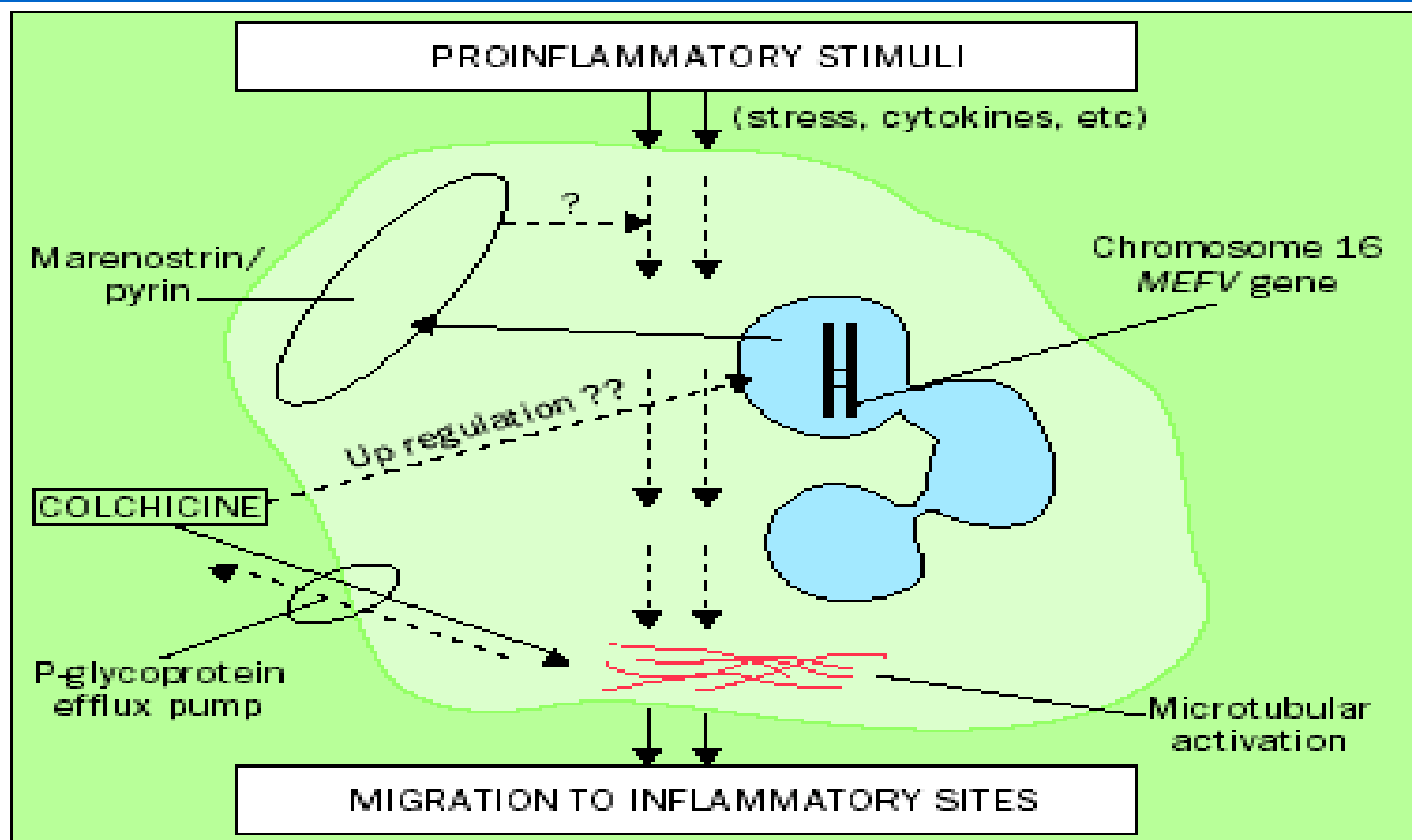
- Homozygous M694V mutations are associated with a severe phenotype
  - Present in 94% of North African FMF patients, also Iraqi Jews and Armenians
  - Earlier onset of disease, more frequent and severe attacks
  - Require higher doses of colchicine
  - Strong preferential association with amyloidosis in studies

# Pathophysiology

- Exact mechanism is unclear
- Disease characterized by high chemotactic activity of neutrophils with massive influx to affected serosa/tissues
- Pyrin/marenostrin involved in down-regulation of inflammatory mediators, may also interfere with neutrophil cytoskeletal functions

# Pathophysiology

- Deficiency of C5a inhibitor also implicated
- C5a is highly potent complement involved in chemotaxis of neutrophils
- Low levels of inhibitor found in peritoneal and synovial fluid from FMF patients
- No clear relationship between lack of inhibitor and MEFV gene
- TNF alpha levels also elevated



**Figure 2: Suggested pathogenesis of FMF**

Polymorphonuclear leucocytes (PMN) are site of action. Ongoing proinflammatory stimuli are normally balanced by marenostrin, a protein encoded by *MEFV* gene and expressed exclusively in mature PMN. Mutation of gene removes host control and allows microtubular activation and migration of PMN to inflammatory sites. Colchicine achieves high concentration in PMN due to deficient P-glycoprotein efflux pump function in these cells. It acts on microtubuli and possibly by upregulating *MEFV* gene expression.

# Secondary Amyloidosis

- FMF is a major cause of AA amyloidosis
- SAA is precursor acute phase circulating protein, AA is deposited in tissues
- Involvement is mainly renal, other organs usually after ESRD
  - thyroid, gastric, hepatic, splenic, cardiac
- Four successive stages of nephropathy: latent, proteinuric, nephrotic and uremic

# Treatment

- Colchicine is an effective treatment for attacks and prevention of amyloidosis
- Study of 45 patients treated with prophylactic colchicine for 15y showed:
  - 72% good response: <1 attack/ 6 mo
  - 15% partial response: <1 attack/ 3 mo
  - 13% failed response
  - another study suggests majority of failure is due to non-compliance

# Prevention of amyloidosis

- Prevalence of amyloid in patients treated with colchicine is estimated at < 5%
- NEJM 1986: largest study of prophylactic use of colchicine
  - Rate of development of proteinuria (9-11y): 1.7% in 960 compliers vs. 49% in 54% compliers
- Prevention of disease progression and reduction in protein excretion with higher doses of colchicine

# ?Role of Interferon alpha

- Pilot study of 7 patients resistant to treatment with colchicine, no RCT
- 21 consecutive attacks were treated with 3-10 million IU s.c. interferon alpha at early onset
- Observed efficacy in 18 of 21 attacks (halted within mean of 3.05h)
- Early administration in prodromal phase seems crucial