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Solving the Diagnostic Puzzle of Hereditary & Periodic Fever Syndromes

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Faculty Disclosure

- Speaker: Abbvie

Objectives

- Review fever and associated differentials
- Review pathophysiology of autoinflammatory syndromes
- Review epidemiology and genetics of fever syndromes
- Review signs and symptoms of fever syndromes
- Review current treatment recommendations
- Discuss prognosis
- Present case studies

Fever

- Most common signs of illness in children
 - Acute: <2-3 weeks
 - URI
 - Chronic: >2-3 weeks
 - Chronic infections
 - Rheumatic diseases
 - Malignancy
- FUO: Sustained daily fever of at least 101°F \geq 8 days

Recurrent Fever

Recurrent febrile episodes lasting a few days to a few weeks

- Common in infants and children attending day care or kindergarten due to viral infections
- Parents often worry about immunodeficiencies
 - Usually these kids also have failure to thrive and other underlying pathology
 - Infections are often unusual or opportunistic
- Frequent localization to the same organ system should raise suspicion of anatomic defects
 - Bronchopulmonary sequestration, Urethral valves

Recurrent or Periodic Fever Syndromes in Children

Differentials

- **Infectious Diseases**
- Rheumatic Diseases
- Hereditary Autoinflammatory Syndromes
- Cyclic Neutropenia
- Idiopathic Conditions

Infectious Causes of Periodic Fevers

- Brucellosis (*Brucella melitensis*, *Brucella abortus*)
 - Ingestion of contaminated, unpasteurized milk or milk products or through contact with infected animals by means of skin abrasion. (*Human infections rare except in areas lacking proper pasteurization*)
- Rat-Bite Fever (*Spirillum minus* – Japan. *Streptobacillus moniliformis* – US)
 - Transmitted by rats
- Relapsing Fever (*Borrelia recurrentis*)
 - Transmitted person to person by ticks

Recurrent or Periodic Fever Syndromes in Children

Differentials

- Infectious Diseases
- Rheumatic Diseases
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- Cyclic Neutropenia
- Idiopathic Conditions

Rheumatic Causes of Periodic Fevers

Some rheumatic disorders can cause unexplained febrile episodes that sometimes conform to the criteria for periodic fever syndromes

- Behcet's Disease
- Relapsing Polychondritis
- Systemic Lupus Erythematosus
- Crohn's Disease

Recurrent or Periodic Fever Syndromes in Children

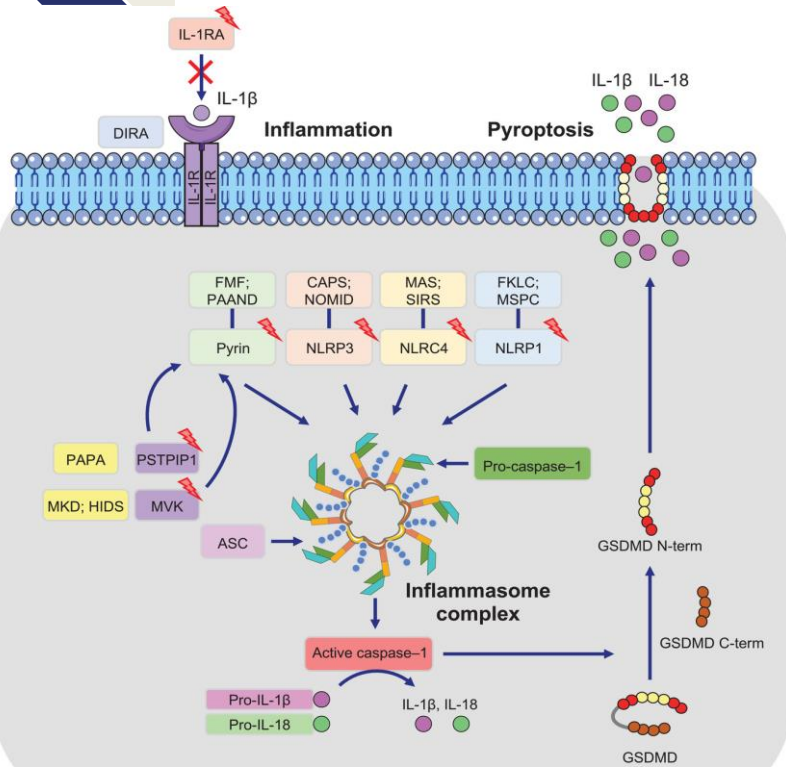
Differentials

- Infectious Diseases
- Rheumatic Diseases
- Hereditary Autoinflammatory Syndromes
- Cyclic Neutropenia
- Idiopathic Conditions

Hereditary Autoinflammatory Syndromes

- Model for autoinflammatory syndromes
 - Recurrent attacks of fevers, serositis & rashes
 - Family member often have similar symptoms
- Affects the innate immune system
- No evidence of autoantigen exposure (not autoimmune)
 - No antibodies or auto-reactive T cells
- Genetically mediated – single mutation (**monogenic**)
- Result: dysregulation of the inflammatory response

Immune Response



Innate Immunity

- 1st responders
 - Cells: Neutrophils, NK cells, macrophages (antigen presenting cells)
 - Proinflammatory Cytokines: IL-1, IL-6, TNF- α (*signal danger*)
 - Complement (*tag foreign proteins*)
 - Activation of inflammasomes
- ### NLRP3 Inflammasome = Caspase-1 complex
- Role is to convert pro-IL-1 β to active IL-1 β
 - Drives production of IL-1

Hereditary or Periodic Fever Syndromes

Consider when/if

- Recurrent infections due to immunodeficiency or organ malformation **excluded**
- Malignancy **excluded**

Pattern Recognition

- Unexplained episodes of fever with a characteristic frequency present
- Characteristic constellation of symptoms present
- 3 or more episodes in a 6-month period

Hereditary Fever Syndromes

- Periodicity: variable between attacks

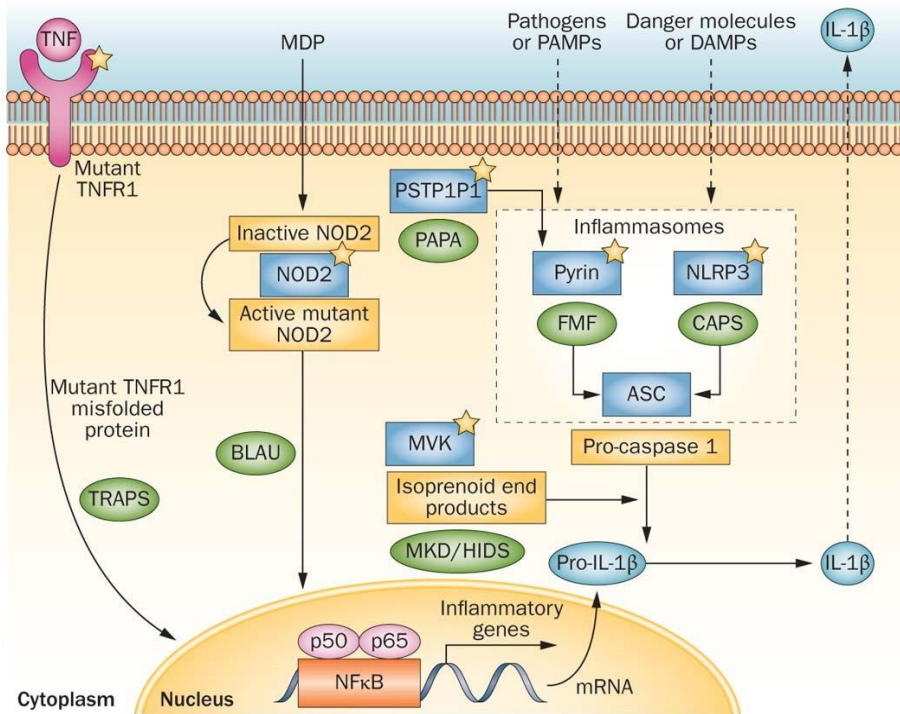
Periodic Fever Syndromes

- Periodicity: fixed between attacks

Hereditary Fever Syndromes

- Familial Mediterranean Fever (FMF)
- Hyperimmunoglobulin D Syndrome (HIDS)
- Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)
- Cryopyrin-associated Periodic Syndromes (CAPS)
 - Familial Cold Autoinflammatory Syndrome (FCAS)
 - Muckle Wells Syndrome (MWS)
 - Neonatal-onset Multisystem Inflammatory Disorder (NOMID)

Familial Mediterranean Fever (FMF)



Most common autoinflammatory syndrome

- Autosomal recessive mutation
- Pathogenic mutation of *MEFV* gene, located on chromosome 16
 - Encodes *pyrin*
 - Immunoregulatory protein
 - Dampens inflammatory response

FMF - Populations at Risk

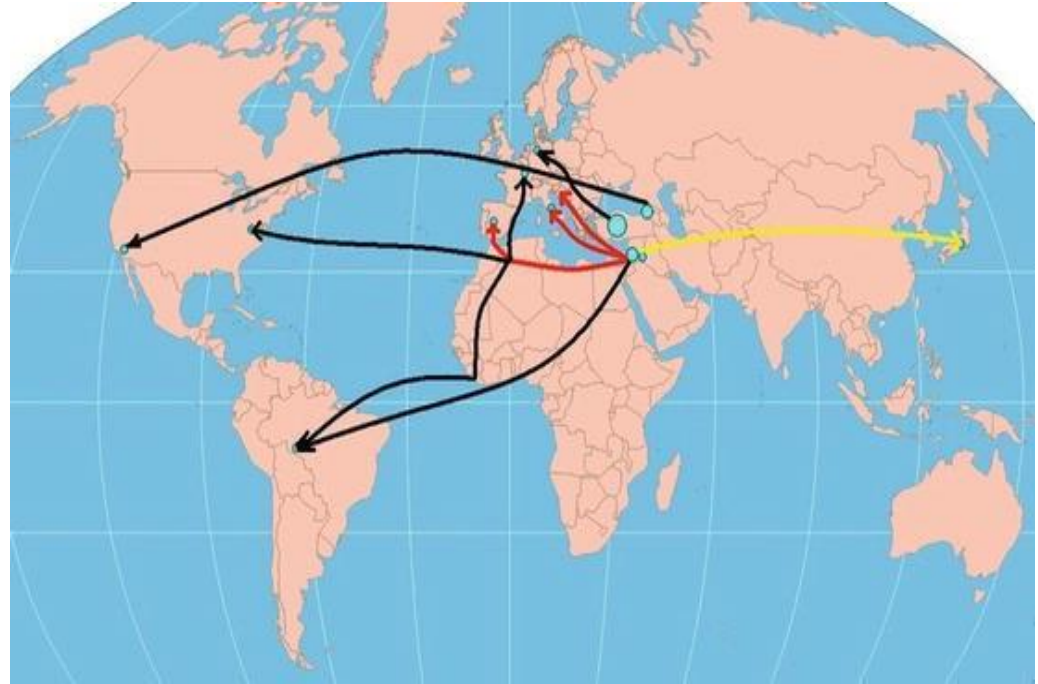
Sephardic Jews

Arab

Armenian

Turkish

- Carrier risk 1:3 to 1:5
 - Evolutionary advantage
- Occurs in lower frequencies in other Mediterranean populations and ethnicities



FMF - Clinical Manifestations

- 1st episode during childhood or adolescence
 - 80% by age 10; 90% by age 20
 - 60% male
 - 60% have affected 1st degree relative
- **Duration of Episodes:** 12-72 hours
- **Between Episodes:** Usually completely well
- **Periodicity:** Days to months
- **Signs/Symptoms:** Inflammation of the peritoneum, pleura, joints, skin or a combination

FMF - Clinical Manifestations

Fever (100%)

- In children, fever may be only signs of FMF, although other symptoms generally develop over time

FMF - Clinical Manifestations

Arthritis (70%)

- Common involvement
- Often 1st sign in children
- Arthralgia more common than arthritis
 - Adults: monoarticular
 - Children: may be polyarticular, symmetrical or asymmetrical, pain, large effusions
- Synovial fluid - sterile, but may have elevated leukocyte counts seen with septic arthritis
 - May have protracted course affecting knees or hips, but rare
 - Radiographs: severe juxta-articular osteoporosis, erosions, osteonecrosis

FMF - Clinical Manifestations

Abdominal Pain (95%)

- Often accompanies fever
- Mild discomfort and distension to severe pain with rigidity
- Constipation more common than diarrhea
 - Extreme case: peristalsis may cease - paralytic ileus
- Generalized or focused to a quadrant, may mimic appendicitis
 - Sterile peritonitis (85%)

FMF - Clinical Manifestations

Pleuritis (30%)

- Generally unilateral
- Decreased breath sounds
- Less common
 - Small effusion, friction rub, atelectasis

FMF - Clinical Manifestations

Skin (7-40%)

- Less common than serosal or synovial involvement
- Erysipeloid erythematous rash on the dorsum of the foot, ankle or lower leg
 - May occur alone or with other manifestations
- Bx: prominent mixed cellular infiltrate



FMF - Clinical Manifestations

Less Common

- Headache
- Unilateral acute scrotal pain in prepubescent boys
- Febrile myalgia
- Diverse cutaneous manifestations: HSP

Rare

- Behcet's disease

May following may also be seen more frequently in FMF patients c/w the general population:

- Polyarteritis Nodosa (PAN)
- Microscopic polyarteritis (MPA)
- Glomerulonephritis
- Inflammatory Bowel Disease (IBD)

FMF - Lab Considerations

During attacks

- Elevated WBC, ESR, CRP, serum amyloid A (SAA), complements

During & between attacks

- Continuous elevation of APRs can lead to the development of AA secondary amyloidosis

SAA deposition occurs in several organs

- Renal failure by age 40 common before effective treatment available

Recommend UA to screen for proteinuria

- If positive, confirm SAA by kidney bx (most sensitive) or rectal bx (less expensive, less invasive, 75% sensitivity)

FMF - Risk of Amyloidosis

Risk of amyloidosis increases:

- Positive family history of SAA
- Male
- α/α genotype at the serum amyloid A1 locus
- Poor adherence with colchicine therapy
- Homozygosity for the M694V mutation
 - Arthritis
 - Erysipeloid erythema
- Greater risk in the Middle East vs. US

FMF - Treatment

Colchicine

- 95% - marked improvement in symptoms
- 75% - near remission of symptoms
- 5-10% - fail (*probably due to nonadherence or intolerance*)
- Reduces risk of amyloidosis from 37% to 5
 - Children < 5: ≤ 0.6 mg/d
 - Children 5-10: 0.6-1.2 mg/d
 - Children > 10 & adults: 1.2-1.8 mg/d

IL-1 antagonist (*unknown effect on amylosis*)

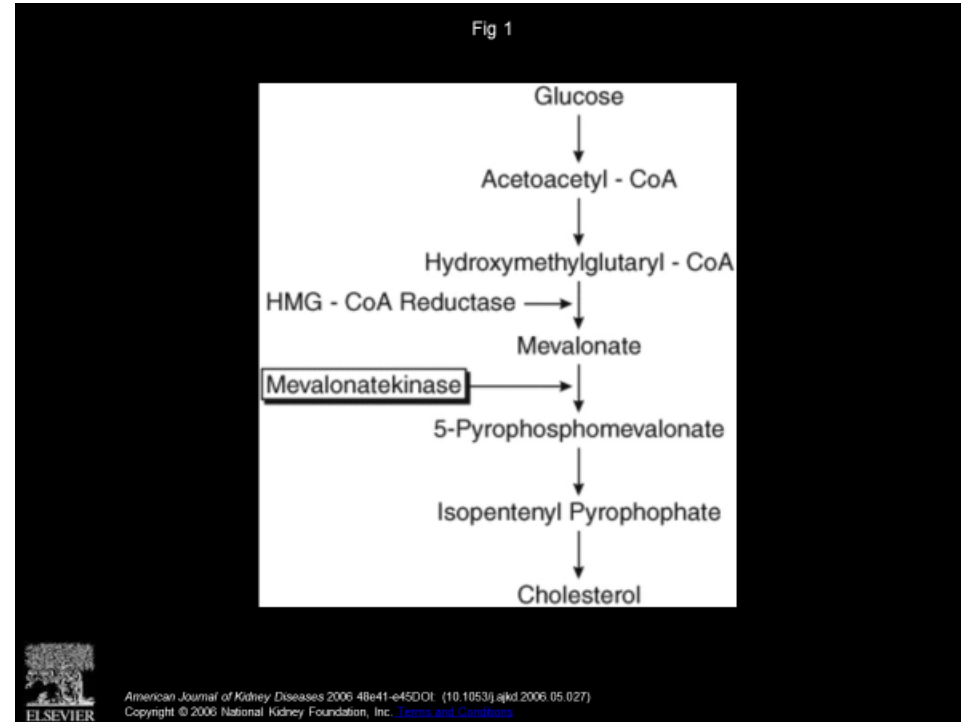
- Canakinumab -anti-IL1- β monoclonal antibody
- Anakinra – IL-1 receptor antagonist
- Rilonicept – dimeric fusion protein that blocks IL-1 receptor

FMF - Outcome & Prognosis

- End-stage renal amyloidosis
 - Transplant is the preferred treatment for renal failure
 - Continue oral colchicine to prevent SAA in the transplanted kidney

Hyperimmunoglobulin D Syndrome - HIDS

- Rare
- Autosomal recessive
- Mutation in the mevalonate kinase (MKV) gene
 - Classic HIDS is due to compound heterozygous or homozygous mutation in the *MVK* gene
 - The underlying genetic defect is not known in Variant HIDS



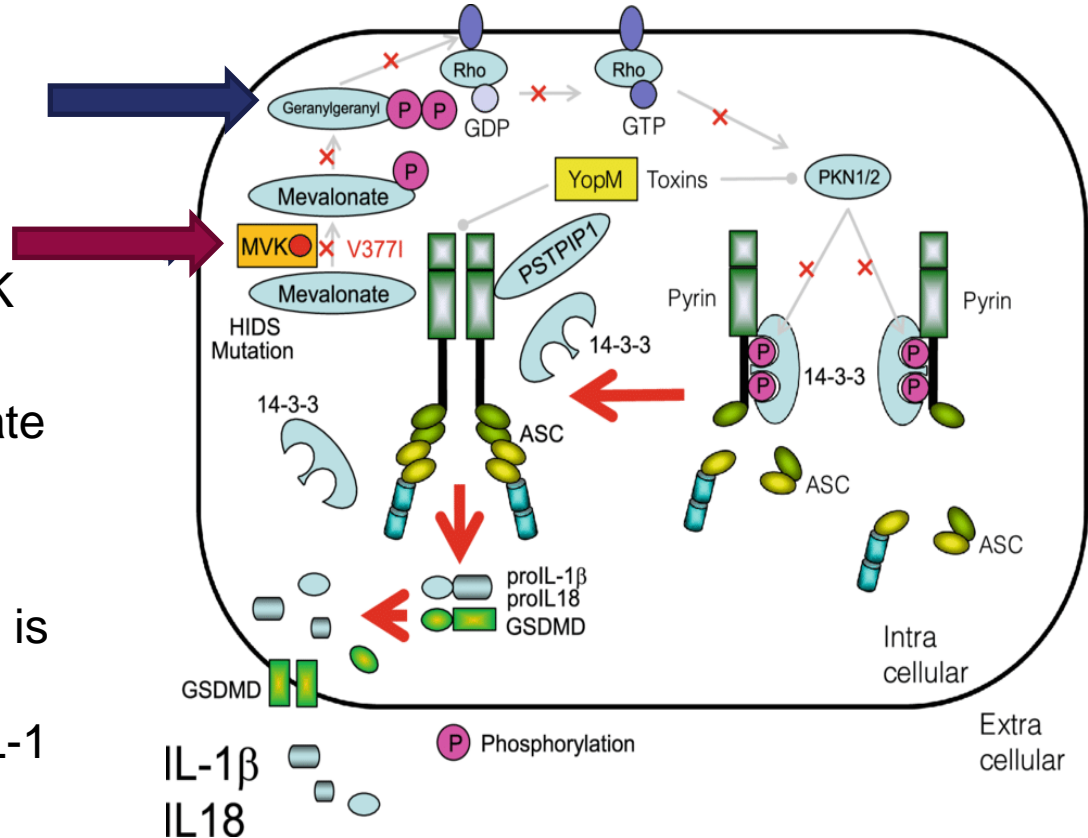
HIDS

Problem with the cholesterol biosynthesis pathway

- Homozygous or compound heterozygous mutation of MVK gene on chromosome 12q24
- **Loss of function** of mevalonate kinase (MVK)

How does this cause fever?

- Geranylgeranylpyrophosphate is a byproduct, stimulates inflammasomes and causes IL-1 production



HIDS - Epidemiology

- Average age of onset: 6 months old
- 70% have 1st episode prior to 12 months of age
- Equally common in males and females
- Mainly northern European ancestry (50% Dutch heritage)
- Attacks often triggered by childhood vaccinations
 - Sustained fever with rashes for 4-5 days every time they get vaccines

HIDS - Clinical Manifestations

Recurrent, unremitting fever (76-100%)

- **Duration of Episode:** 4-7 days
- **Between episodes:** normal
- **Periodicity:** 4 weeks, variable

Signs/Symptoms

- Cervical lymphadenopathy (94 %)
- Erythematous macular rash (80%)
- Abdominal pain (70-80%)
- Arthritis (60-80%)
- Headache (70%)



HIDS - Labs

- Elevated serum IgD
 - Normal levels do not exclude the disease
- Elevated serum IgA
- Elevated urinary mevalonic acid, urinary leukotriene E4
- Increased APRs (CRP, ESR, Ferritin, serum amyloid A)
- Leukocytosis (predominantly neutrophils)

HIDS - Treatment & Prognosis

Treatment

- NSAIDS – 1st line, mildly effective
- Corticosteroids – 1 mg/kg/d for 4-7 days
- Anti-IL-1 therapy:
 - Anakinra: short acting, dosed once daily, “on demand” or prophylactically
 - Canakinumab: long acting, dosed q 4-12 wks, used prophylactically

Prevention

- TNFi (etanercept), IL-6i (tocilizumab)

Prognosis

- May decrease in severity and frequency over time
- Low risk of amyloidosis (<10 cases)

Tumor Necrosis Factor Receptor-1 Associated Periodic Syndrome (TRAPS)

- Rare
- Most prevalent autosomal dominant hereditary fever syndrome 1: 1 million
 - Pathologic variant 55 kDa receptor for TNFRS1
 - Incomplete penetrance
- No ethnic predilection
- Median age of onset: 3 years old
- Male predominance (3:2)

TRAPS - Clinical Manifestations

- Fever >5 days
- Associated with
 - Severe myalgia (100%)
 - Migratory, erythematous patch over area of myalgia
 - Rash (63%) – may spread distally over time
 - Abdominal pain (92%)
 - Conjunctivitis or periorbital edema (82%)
 - Pleuritic chest pain (57%)
 - Testicular pain
- Duration of Episode: 5-14 days
- Periodicity: every 5-6 weeks, can vary

TRAPS - Treatment & Prognosis

Treatment for typical attacks

- NSAIDS
- Systemic corticosteroids 1 mg/kg @ onset and taper over 7-10 days

Treatment for frequent or severe attacks *(or variant with high risk for SAA)*

- IL-1 antagonist, 1st line (canakinumab)
- Etanercept *(binds bound & unbound TNF)*
 - Reduction in number of attack and total steroid dose

Prognosis

- Amyloidosis: 2-25%

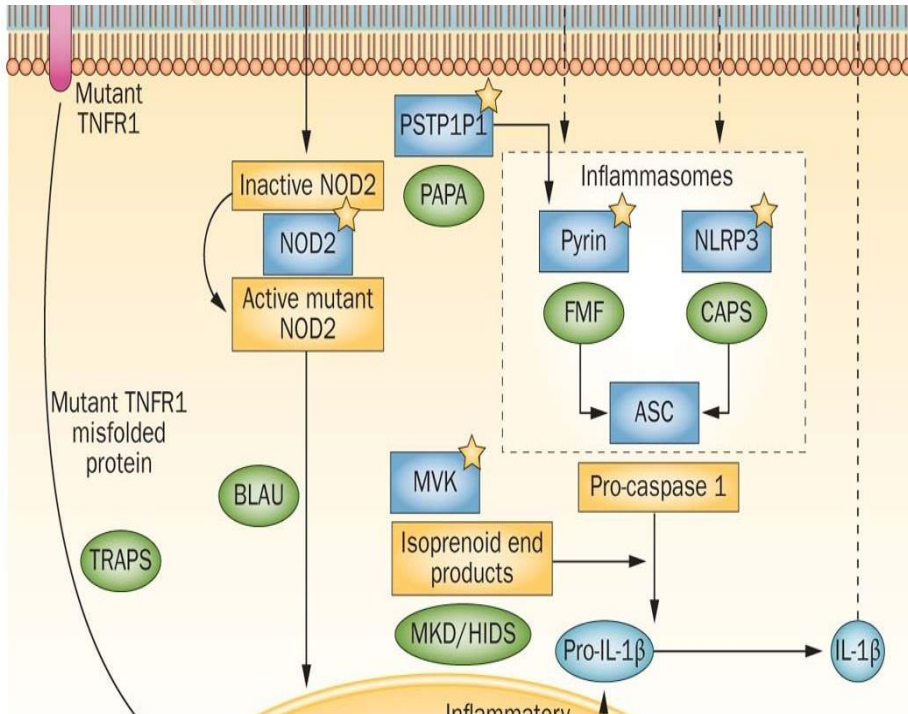


Cryopyrin-Associated Periodic Syndromes (CAPS)

3 clinically similar, dominantly transmitted syndromes caused by a mutation of a single gene

- Familial Cold Autoinflammatory Syndrome (FCAS)
- Muckle-Wells Syndrome (MWS)
- Neonatal-onset Multisystem Inflammatory Disorder (NOMID)

CAPS - Epidemiology

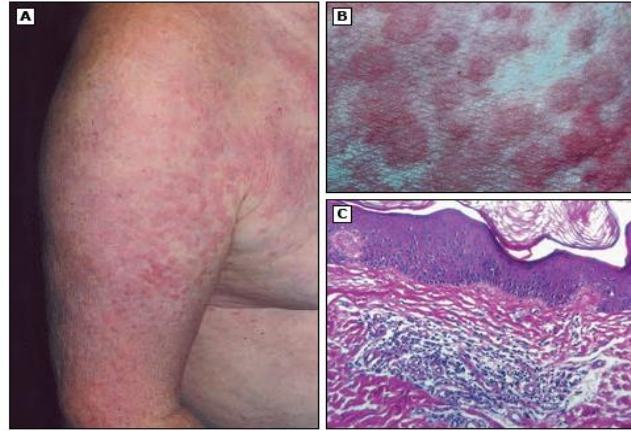


- Autosomal dominant
 - Variable penetrance
- Pathologic mutation of NLRP3, at chromosome 1q44
 - Encodes cryopyrin

Familial Cold Autoinflammatory Syndrome (FCAS)

- Mildest form
- Generalized cold results in typical systemic inflammatory response: fever, urticarial rash, conjunctival injection, arthralgias
- Symptoms begin 1st year of life
 - Fever starts 7 hours after cold exposure
 - Leukocytosis starts 10 hours after cold exposure, subsides 12-14 hours later (>30K)
 - **Duration of Episode:** 24 hours, variable
 - **Between Episodes:** may have daily rash, fatigue, headache, myalgias (afternoon and evening)

Adult familial cold autoinflammatory syndrome rash



(Panels A and B) A typical urticarial rash on the patient's right arm.

(Panel C) Skin biopsy specimen from the left shoulder shows moderate superficial and minimal deep perivascular chronic inflammation with interstitial neutrophils and mononuclear cells (hematoxylin and eosin, original magnification $\times 20$).

From: Shpall RL, Jeffes EW, Hoffman HM. A case of familial cold autoinflammatory syndrome confirmed by the presence of a CIAS1 mutation. *Br J Dermatol* 2004; 150(5):1029-31.

<https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2133.2004.05927.x>

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Muckle-Wells Syndrome(MWS)

Triad of signs/symptoms

- Intermittent episodes of fever, headache, urticarial rash, and joint pain (arthralgias or arthritis)
- Progressive sensorineural hearing loss
- Secondary (AA) amyloidosis with nephropathy

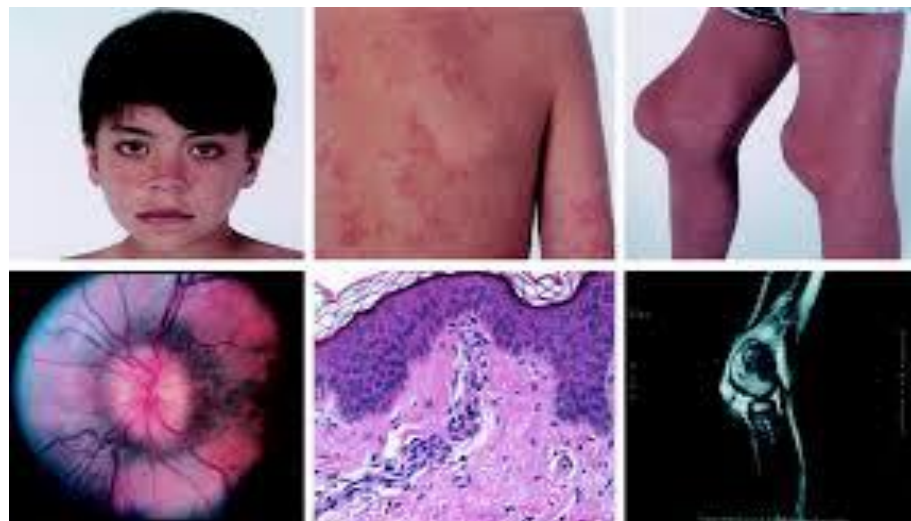
Trigger may include both heat and cold

Duration of Episodes: 12-36 hours

Periodicity: Every few weeks

Neonatal-Onset Multisystem Inflammatory Disease (NOMID)

- Most severe
- Clinical features at or near birth
 - Migratory, erythematous rash/urticaria
 - Fever
 - Impaired growth
 - Abnormal facies with frontal bossing
 - Protruding eyes
 - Saddle-shaped nose
- Chronic meningitis
- Sensorineural hearing loss
- Cerebral atrophy
- Uveitis
- Lymphadenopathy
- Hepatosplenomegaly
- Limb/joint pain
- Exuberant cartilaginous proliferation at growth plates
- Premature death
- Secondary (AA) amyloidosis



CAPS - Treatment

NSAIDS

Systemic corticosteroids

IL-1 receptor antagonists – helps within the first 6 hours of 1st dose

- Anakinra 1-2 mg/kg daily, max 8 mg/kg daily
 - FDA approved for NOMID
 - Also used for FCAS and MWS
 - Helps with symptoms, preventatively and to reduce risk of amyloidosis
 - May be superior to canakinumab for control of CNS symptoms given its ability to penetrate the blood-brain barrier

The Eurofever/PRINTO classification criteria for hereditary recurrent fevers and their performance

Cryopyrin-associated periodic syndromes	Familial Mediterranean fever	Tumor necrosis factor receptor-associated periodic fever syndrome	Mevalonate kinase deficiency
<p>Presence of a confirmatory <i>NLRP3</i> genotype* and at least 1 among the following:</p> <ul style="list-style-type: none"> Urticarial rash Red eye (conjunctivitis, episcleritis, uveitis) Neurosensory hearing loss <p>OR</p> <p>Presence of a not confirmatory <i>NLRP3</i> genotype† and at least 2 among the following:</p> <ul style="list-style-type: none"> Urticarial rash Red eye (conjunctivitis, episcleritis, uveitis) Neurosensory hearing loss 	<p>Presence of a confirmatory <i>MEFV</i> genotype* and at least 1 among the following:</p> <ul style="list-style-type: none"> Duration of episodes 1 to 3 days Arthritis Chest pain Abdominal pain <p>OR</p> <p>Presence of a not confirmatory <i>MEFV</i> genotype^Δ and at least 2 among the following:</p> <ul style="list-style-type: none"> Duration of episodes 1 to 3 days Arthritis Chest pain Abdominal pain 	<p>Presence of a confirmatory <i>TNFRSF1A</i> genotype* and at least 1 among the following:</p> <ul style="list-style-type: none"> Duration of episodes ≥ 7 days Myalgia Migratory rash Periorbital oedema Relatives affected <p>OR</p> <p>Presence of a not confirmatory <i>TNFRSF1A</i> genotype† and at least 2 among the following:</p> <ul style="list-style-type: none"> Duration of episodes ≥ 7 days Myalgia Migratory rash Periorbital oedema Relatives affected 	<p>Presence of a confirmatory <i>MVK</i> genotype* and at least 1 among the following:</p> <ul style="list-style-type: none"> Gastrointestinal symptoms Cervical lymphadenitis Aphthous stomatitis
Sensitivity: 1	Sensitivity: 0.94	Sensitivity: 0.95	Sensitivity: 0.98
Specificity: 1	Specificity: 0.95	Specificity: 0.99	Specificity: 1
Accuracy: 1	Accuracy: 0.98	Accuracy: 0.99	Accuracy: 1

A patient with evidence of elevation of acute phase reactants (ESR, CRP, or SAA) in correspondence to the clinical flares and careful consideration of possible confounding diseases (neoplasms, infections, autoimmune conditions, other inborn errors of immunity) and a reasonable period of recurrent disease activity (at least 6 months) is classified as having hereditary recurrent fever if the criteria are met.

PRINTO: Paediatric Rheumatology International Trials Organisation; *NLRP3*: NLR family pyrin domain-containing 3; *MEFV*: MEFV innate immunity regulator, pyrin; *TNFRSF1A*: TNF receptor superfamily member 1A; *MVK*: mevalonate kinase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SAA: serum amyloid A.

* Pathogenic or likely pathogenic variants (heterozygous in autosomal-dominant diseases; homozygous or in trans [or biallelic] compound heterozygous in autosomal-recessive diseases).

† Variant of uncertain significance (VUS). Benign and likely benign variants should be excluded.

Δ In trans compound heterozygous for one pathogenic *MEFV* variants and one VUS, or biallelic VUS, or heterozygous for one pathogenic *MEFV* variant.

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Recurrent or Periodic Fever Syndromes in Children

Differentials

- Infectious Diseases
- Rheumatic Diseases
- Hereditary Autoinflammatory Syndromes
- **Cyclic Neutropenia**
- Idiopathic Conditions

Cyclic Neutropenia - CN

- Rare, 1:1 million
- Autosomal dominant
 - Pathologic variant of ELAINE, the gene that encodes neutrophil elastase
- Occurs in children and adults
- Periods of severe neutropenia that recurs
 - Febrile episodes due to periodic granulocytopenia
 - Intervals of normal granulocyte counts

CN - Clinical Manifestations

- Early childhood
- Duration of Episode: 3-10 days
- Between Episodes: usually well
- Periodicity: 14-36 days, but usually every 21 days
- During attacks: ANC less than 500/dL (may be 0) on 3-5 consecutive days
 - While neutropenic: susceptible to infection from normal flora

Signs/symptoms

- Oral ulcers, gingivitis, fever, malaise, lymphadenopathy

CH - Treatment

- Granulocyte colony-stimulating factor (G-CSF)

Recurrent or Periodic Fever Syndromes in Children

Differentials

- Infectious Diseases
- Rheumatic Diseases
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- Idiopathic Conditions

Periodic Fever with Aphthous Stomatitis, Pharyngitis and Adenitis (PFAPA)

- Most common periodic fever syndrome in children
- Autoinflammatory
 - No autoantibodies or autoreactive T cells
- Onset in early childhood (<5 years old)
- Male predominance
- Familial predisposition
- Etiology unknown, likely **polygenic** and complex

PFAPA - Clinical Manifestations

- Onset usually before age 5
- **Duration of Episodes:** 5 days
 - Max temp usually reached within the 1 day and end abruptly or settle down over 1-2 days
- **Between Episodes:** Healthy
- **Periodicity:** Predictable febrile episodes every 28 days (26-30)
- Growth and development is normal
- “Aha” moment - malaise, fatigue, oral lesion herald onset of cycle

PFAPA - Clinical Manifestations

- Pharyngitis (~60%)
- Cervical adenopathy (~60%)
- Oral aphthae (~60%)
- Abdominal pain (~60%)
- Headaches
- Myalgias/arthralgias

Aphthous ulcers

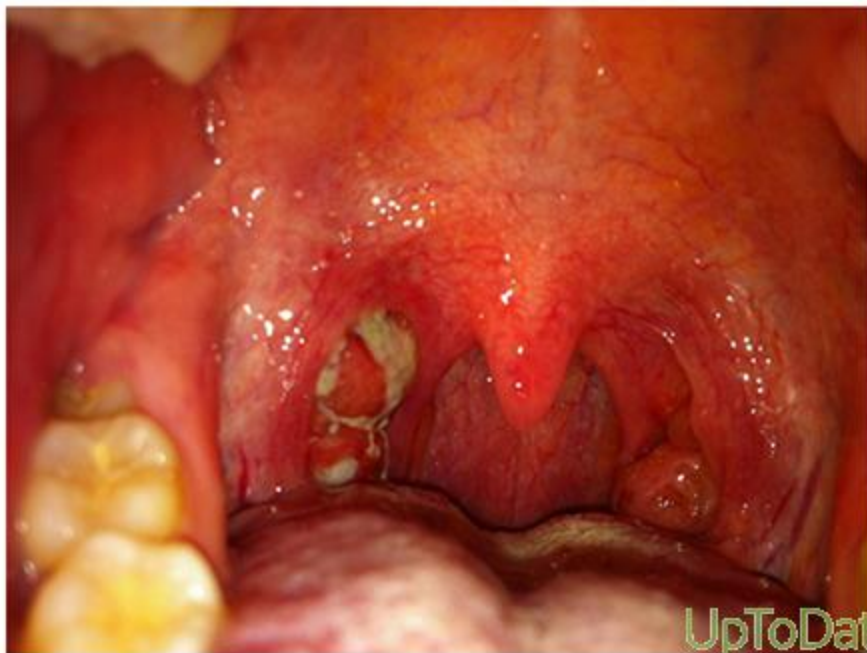


Round, yellow-gray ulcers are present on the oral mucosa.

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Pharyngitis in a patient with periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome



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PFAPA - Labs

During Episodes:

- Elevated total WBC
- Elevated APRs
- Mild elevation in IgG, IgM, IgA
- Increase in serum levels of interferon-gamma, TNF and IL-6

PFAPA - Diagnosis

Marshall Criteria

10-year registry, 94 PFPAP pts

- Regularly recurring fevers at an early age at onset (<5 years of age)
- Constitutional symptoms in the absence of URI with at least one of the following
 - Aphthous stomatitis
 - Cervical adenitis
 - Pharyngitis
- Exclusion of cyclic neutropenia and known hereditary periodic fever syndromes
- Asymptomatic intervals between episodes
- Normal growth and development

PFAPA - Treatment

Acute Treatment

- Acetaminophen or NSAIDs
 - Cycles will return
- Glucocorticoids - if started early, may abort attacks.
 - Single dose may be effective, some may require treatment for 3-4 days
 - May result in shortened interval between attacks
 - 1-2 mg/kg (max 60 mg) as single dose or divided over 2 doses

Prevention

- Cimetidine 20-40 mg/kg/d in divided doses
- Colchicine 0.5-1.2 mg/d (4-6 yrs old). 1-1.8 mg/d (>6 yrs old)
- Tonsillectomy - may eliminate attacks

PFAPA: Tonsilectomy as Treatment

Prospective cohort study of 94 patients diagnosed with PFAPA

- Age 1-17
- Seen at Rady Children's Hospital in San Diego, California
- 63 patients had tonsillectomy (with or without adenoidectomy)
 - 44 pts had complete resolution of symptoms after surgery
 - ~ 2 months
 - 3 patients had a relapse

Conclusion: Tonsillectomy is an effective surgical treatment option

PFAPA: Consensus Treatment Plan (CARRA) – 2020

Purpose: Develop a consensus treatment plan and response criteria for PFAPA

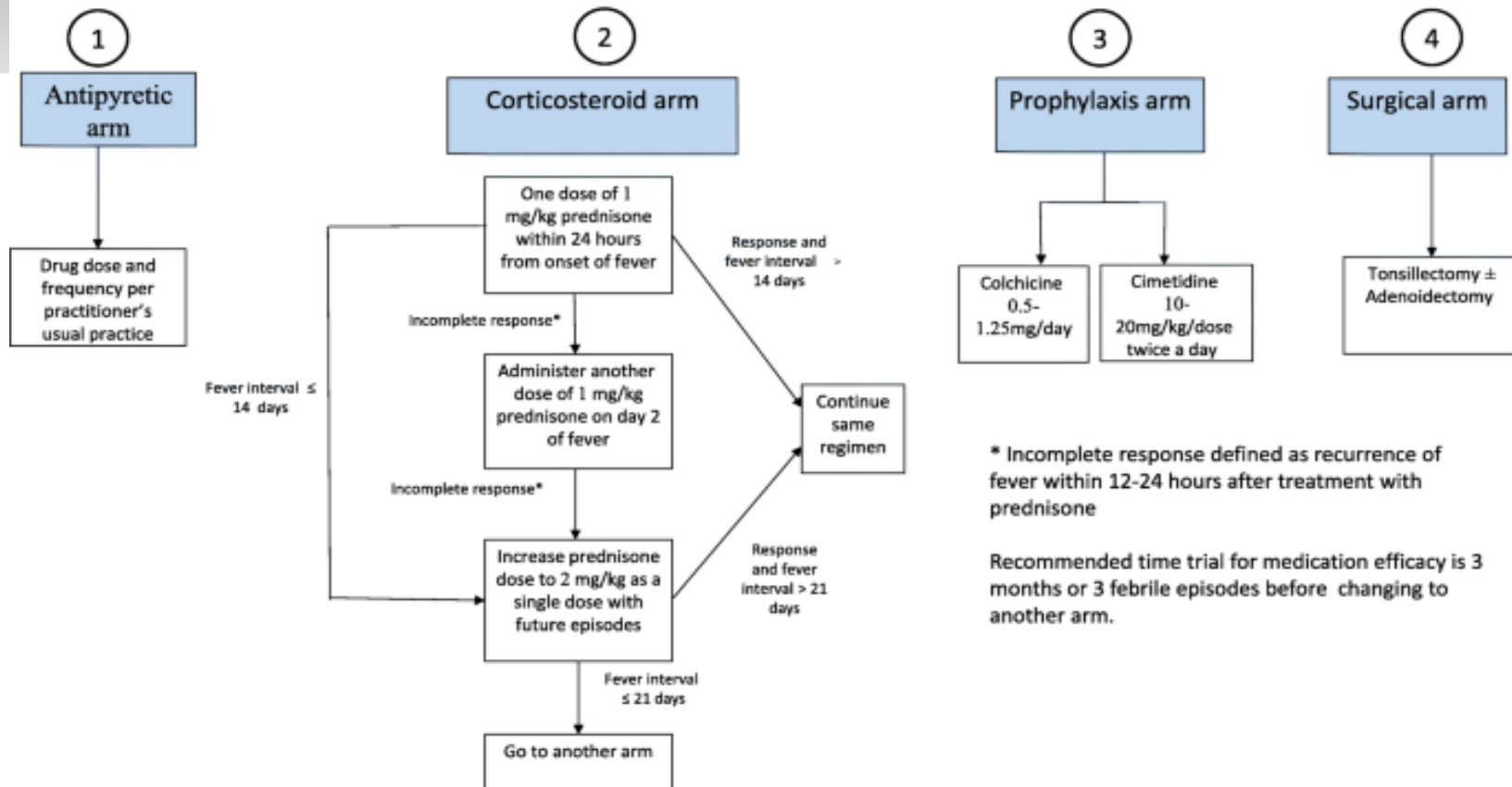
Working Group: North American, European, Israel pediatric rheumatologist, pediatric infectious disease specialists, otolaryngologists and allergist/immunologists with expertise in PFAPA (2014-2018)

- 100 CARRA members selected at random to follow at least 1 treatment arm during a future pilot study looking at direct comparison of outcomes in each treatment arm

Recommended starting with 1 of 4 treatment arms

- Antipyretic
- Abortive/Corticosteroid
- Prophylaxis
- Surgical

Choose 1 out of 4 arms



PFAPA - Flares During Covid

- Can emotional stress trigger flares?
 - 99 pediatric pts with active PFAPA enrolled, two Israeli center
 - 3-12 years old
 - Stressful time period: Covid-19 pandemic restrictions in place
 - Less stressful time period: Covid-19 pandemic, less restrictions
 - 41 reported at least 1 flare during preceding 2 weeks compared to 24 in the less stressful period

Case Study 1

- 5-year-old male
- Admitted to hospital for limping and periodic fever
- FHx: Same symptoms in 3-year-old brother
- PMH:
 - Similar symptoms since he was 3 months old, for both, after first vaccination
 - Monthly fever for 3-6 days associated with lymphadenopathy, abdominal pain with vomiting and diarrhea, maculopapular rash

Case Study 1

PE:

Anterior cervical lymphadenopathy, maculo-papular rash and arthritis with swelling to right knee

Labs:

- WBC elevated at 15K, 82% segs
- Elevated ESR, CRP, IgA, Serum Amyloid A
- IgD normal
- ANA neg

Genetic Testing:

- Deletion on chromosome 12: Compound heterozygous for 1268T e V3771 mutations
 - HIDS

Treatment:

- Colchicine 1 mg/d

Case Study 2

- 8-year-old Korean male, presented to hospital
- Generalized edema x 2 weeks
- Sudden onset scrotal swelling 2 days ago
- Hx of recurrent, acute, self-limited episodes of fever at varying intervals with elevated APRS
 - Through work up unrevealing
 - Working dx: JIA, even though no joint symptoms
- FHx: father died of MI at age 40, no hx of renal disease, periodic fever or auto-inflammatory disease

Case Study 2

VS:

T 101.2 F. BP 108/75.

Wt: Increased from 23 kg to 26 kg in 2 weeks

PE:

Pretibial edema

Swollen abdomen

No rash

Lab:

CRP high 140 mg/L

Hgb low 8.4 g/dL

Albumin low 1.0 g/dL, Fibrinogen high 1029 mg/dL

24-hr Urine prot/cr – nephrotic 14.49

ANA, anti-cardiolipin ab neg

Complement wnl

Immunoglobulins wnl

Case Study 2

Imaging:

- Abd US: Slightly increased renal parenchymal echogenicity with splenomegaly, no hydrocele
- Abd CT: enlarged bil kidneys, a well-enhancing mass lesion in the right common iliac chain, lymphadenopathy of small bowel mesentery, small amt of ascites

- Echo: minimal pericardial effusion

Pathology:

- Renal bx: amyloidosis AA
 - Monoclonal gammopathy ruled out

Case Study 2

Dx:

- Presumed FMF: typical attacks, pleuritis, fever, abdominal pain

Treatment:

- Colchicine

Genetic testing:

- DNA analysis of the MEFV gene: 2-point mutations identified (p.PRO258SER, p.ARG408Gln)
- 40% of pts with clinical symptoms of FMF have negative DNA results

Summary

- Autoinflammatory conditions result from dysregulation of the innate immune system leading to increased production of IL-1
- Diagnosis of autoinflammatory syndromes is based on history and response to therapy
 - Sensitivity of genetic testing ~70%
 - We have more work to do
- Treatment of autoinflammatory syndromes is primarily aimed at inhibition of proinflammatory cytokines



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