Introduction

The term *autoinflammatory disease* describes idiopathic inflammatory conditions associated with disorders of the innate immune system; they are not associated with autoantibodies. In contrast, *autoimmune diseases* describes conditions that are typically associated with B cell and T cells of the adaptive immune system and autoantibodies often are found. Autoinflammatory diseases can be inherited or acquired.

The following cases describe two autoinflammatory disorders.

Case 1

History / Physical Examination

Presenting Patient

The patient is a 15-year-old female with an 8-year history of monthly episodes of fever, rash (described as nonintchy hives on the trunk), red eyes, severe headache, and joint pain. Her episodes usually last 2 to 3 days.

Between episodes, the patient generally feels better but still has occasional headache and joint pain. No specific triggers for her episodes have been identified, but they occur more frequently in winter (she lives in a cold climate) and after minor trauma or stress, such as the beginning of a school year.

The physical evaluation identifies positive meningeal signs, conjunctival injection, hive-like rash on the trunk, and mild effusion in large joints.

Diagnostic Tests

Laboratory tests results show high erythrocyte sedimentation rates (ESR) and C-reactive protein (CRP) during episodes (see Table 1). Between episodes, the readings decline but do not normalize. A complete blood count shows anemia, leukocytosis, and thrombocytosis. Urinalysis is normal.
Table 1. Basic Laboratory Test Results

Erythrocyte sedimentation rate
- During attacks: 70 mm/hr
- Between attacks: 35 mm/hr
C-reactive protein
- 7.5 mg/dL during attacks
- 2.5 mg/dL between attacks
Hemoglobin: 11.5 g/dL
White blood cell count: 15,000/µL
Platelet count: 565 x 10³/µL
Urinalysis: protein 2-plus

Before referral, the patient was treated with various nonsteroidal anti-inflammatory drugs (NSAIDs), which provided some relief from her fever and headaches. She was also treated with corticosteroids but needed gradually increased doses. The only drug effective for alleviating her symptoms and prolonging the interval between episodes was intravenous immunoglobulin.

Based on this clinical scenario, which protein mutation is indicated?

a. Mevalonate kinase
b. TNF receptor
c. Pyrin
d. Cryopyrin
e. Proline-serine-threonine phosphatase interacting protein 1

d. Correct.

Clinically, her episodes of recurrent rash, fever, severe headache, and conjunctivitis — symptoms that began in early childhood — indicate a diagnosis of cryopyrin-associated periodic syndrome (CAPS). To confirm the diagnosis, a gene test for the CIAS1 (also called NALP3 or NLRP3 gene) is available at commercial laboratories specializing in genetic testing.

Her clinical presentation eliminated the other syndromes.

- Mevalonate kinase is mutated in hyper IgD syndrome, which starts in the first year of life and causes rash and abdominal pain. Episodes are often triggered by vaccinations.
- Episodes of TRAPS (TNF-receptor-associated periodic syndrome) are usually longer (more than 1 week), the rash is a painful, migratory, erythematous rash and patients have serositis, severe abdominal and/or chest pain that is not present in this patient.
- Pyrin protein mutation occurs in familial Mediterranean fever (FMF), a syndrome that primarily affects ethnic groups originating from the Mediterranean sea area. In FMF, the rash is an erysipelas-like rash, usually in the ankle/foot; serositis is
the major feature and headaches are less prominent. Eyes are rarely involved. The ancestry of FMF is typically from Mediterranean countries.

- Proline-serine-threonine phosphatase interacting protein 1 is the mutated gene in pyogenic arthritis, pyoderma gangrenosum, and the acne (PAPA) syndrome, a rare genetic disorder characterized by severe scarring acne, skin ulcers, and arthritic joints that mimic septic joints. The gene seems to cause disease via a mechanism similar to FMF.

**Differential Diagnosis**

Diagnosis of CAPS is often missed owing to the rarity of these conditions (low index of suspicion). Furthermore, some symptoms of CAPS may be similar to those seen in more common diseases, such as acquired cold urticaria, systemic juvenile idiopathic arthritis, urticarial vasculitis (also rare), and systemic lupus erythematosus.

A number of factors may be considered to help differentiate CAPS from more common diseases:

- Rash (localized vs generalized) and response to antihistamine therapy;
- Autoinflammatory disorders lack the high levels of autoantibodies and autoreactive T cells observed with autoimmune disease;
- Autoinflammatory diseases have a more specific inheritance pattern (autosomal dominant vs sporadic manifestation, although it can have sporadic manifestation in de novo mutations);
- Age at first presentation (infancy vs childhood/adulthood);
- History of occurrence of episodes (throughout life vs spontaneously with resolution within months or years);
- Length of time from cold exposure to symptom onset (hours vs minutes);
- Duration of episodes (hours to 2 days vs minutes to several hours);
- Result of diagnostic ice cube test (negative in CAPS – the general exposure to cold is important vs positive test in acquired cold urticaria);
- Biopsy of the lesions are also helpful. In CAPS there is a predominance of neutrophils as opposed to other types of urticaria in which mast cells and edema are characteristic;
- Laboratory tests show the presence of leukocytosis with white blood cell counts of up to 36,000/mm³ as well as chronically elevated erythrocyte sedimentation rates and acute-phase reactants including serum amyloid A and C-reactive protein.

Genetic testing to sequence the CIAS1/NALP3/NLRP3 gene should be considered to secure a definitive diagnosis. However, absence of the genetic mutation does not rule out CAPS as up to 50% of cases do not have a detectable genetic mutation. Other rare autoinflammatory conditions to consider include familial Mediterranean fever, Hyper-IgD Syndrome, and TNF Receptor-Associated Periodic Syndrome.
**Natural History**

The cryopyrin-associated periodic syndromes (CAPS) consist of three hereditary periodic fever syndromes:

- familial cold-induced autoinflammatory syndrome (FCAS),
- Muckle–Wells syndrome, and
- chronic infantile neurological, cutaneous, articular (CINCA) syndrome, also known as neonatal-onset multisystem inflammatory disease (NOMID).


These syndromes are usually caused by autosomal-dominant mutations in the CIAS1 gene, a constituent of inflammasome, which is involved in the activation of proinflammatory cytokines IL-1β. Male and female offspring are equally affected. Between 50% and 80% of CAPS cases are associated with a CIAS1 gene mutation. ¹
The CAPS are rare disorders. The prevalence is approximately 1 in 500,000 people in the United States. An estimated 600 cases of FCAS and MWS are known in the United States.

Typically, an FCAS episode occurs after exposure to generalized cold (not direct contact with a cold item such as an ice cube). Symptoms usually develop within 2 to 3 hours and include low-grade fever, chills, hivelike rash, arthralgia, myalgia, conjunctivitis, and headaches. Episodes peak after 6 to 8 hours and resolve within 24 hours.

The syndrome develops at birth or within the first 6 months of life in 95% of patients. Interestingly, the infiltrates are polymorphonuclear cells and not mast cells like typical hives, so a skin biopsy can be helpful in the differential diagnosis. Patients have increased acute inflammatory reactants, mostly during attacks. Development of amyloidosis is rare.

The Muckle-Wells syndrome is characterized by longer episodes of recurrent fever than FCAS, usually lasting approximately 3 days. Symptoms include fever, chills, painful joints, and rash. It may also have more significant eye involvement, such as episcleritis and uveitis. During episodes, patients have more severe headaches and meningeal inflammation, so a lumbar puncture is sometimes helpful to identify pleocytosis in the cerebrospinal fluid. Sensorineural hearing loss is observed in 50% to 70% of patients. Amyloidosis develops in about 25% of cases.

The NOMID/CINCA syndrome has an early onset (often at birth), characterized by cutaneous symptoms (eg, persistent, nonpruritic migratory urticaria), fever, central nervous system involvement (chronic meningeal inflammation), and arthropathy. Morphologic changes include short stature, frontal bossing, macrocephaly, saddle nose, and short and thick arms and legs with clubbed fingers. (See Figures)

The most important conditions associated with NOMID/CINCA are chronic meningeal inflammation and arthropathy. The meningeal inflammation typifies the central nervous system involvement and results in hydrocephalus, spasticity in seizures, developmental
delay, mental retardation, and severe headaches. Sensorineural effects include uveitis, conjunctivitis, papillitis, papilledema, and visual loss; hearing loss may also occur.

Arthritis is the primary musculoskeletal symptom associated with NOMID/CINCA. It is mostly a cartilage defect, rather than synovitis, in the epiphysis and the metaphyses. The joint space is relatively unaffected. Significant bony overgrowth occurs that can develop into cartilage tumors.

**Cryopyrin Gene Encoding**

The inflammasome, an essential component of the innate immune system, is a complex system of proteins critical in detecting and responding to microorganisms. It is believed that the inflammasome acts as an early warning system to activate the body's defense system in anticipation of invasion. When these proteins are stimulated, they cue the ultimate production of proinflammatory cytokines.

One such protein, Cryopyrin, is encoded by the CIAS1/NALP3/NLRP3 gene. When stimulated, it interacts in a complex cascade of events that eventually produce proinflammatory cytokines. Cryopyrin is encoded by the CIAS1/NALP3/NLRP3 gene on the 1q44 chromosome, which is primarily exhibited in the cytoplasm of peripheral leukocytes and chondrocytes. Mutations of this gene can stimulate events that ultimately result in increased release of the cytokine IL-1β, which causes the inflammation seen in CAPS.

However, there are different mutations, some of which are specific for certain phenotypes and some overlap. Plus, approximately 30% to 50% of patients with Muckle-Wells syndrome or NOMID/CINA do not have a CIAS1 gene mutation. As a result, CAPS diagnosis is often a clinical diagnosis.

**Treatment**

Which biologic therapy is the most likely to be effective for this patient?

- a. Anti-B cell
- b. Anti-C cell
- c. Anti-TNF
- d. Anti-IL-1  \[ \text{Correct.} \]
- e. Anti-IL-6

Attempts to treat CAPS with anti-inflammatory drugs or immunosuppressants have generally been disappointing, creating a need for novel therapies. Because of the IL-1 component, therapies that block IL-1 have been investigated.

Study results have generally been dramatic. An in vitro study showed that in patients with cryopyrin mutations, treatment with an IL-1–receptor antagonist normalizes the IL-1
pathway, which is bypassed in these patients. In another study, treatment with an IL-1–receptor antagonist prior to the cold exposure decreased serum levels of IL-6 more than IL-1. Even patients with CAPS but without the gene mutation respond to anti-IL-1 therapy.

Several anti-IL-1 therapies are available and/or under investigation (see Table 2 on next page).

**Table 2. Anti-IL-1 Therapies for CAPS**
Click the drug title to read more.

**Four types of anti-IL-1 therapy exist:**
1. Anakinra is an IL-1 receptor antagonist; it was the first of this class marketed.
2. Rilonacept is a fusion protein designed to neutralize circulating IL-1 before it can attach to cell-surface receptors and trigger inflammation.
3. Canakinumab is an anti-IL-1b antibody being investigated for a variety of autoinflammatory diseases. Data from phase II trials in CAPS patients showed that a single dose achieved complete and long-lasting clinical remission that lasted an average of 115 days.
4. Anti-IL-1 receptor antibodies. Caspase-1 inhibitors are a second category of treatments but have only shown limited effects in vitro.

**Anakinra**
In a National Institutes of Medicine study of anakinra in patients with NOMID/CINCA, the agent markedly decreased most clinical symptoms, inflammation, and steroid dosing while improving function. It had less effect on arthropathy and cognitive function. In addition, patients had significant weight gain, most likely related to the effect on chronic inflammation. It has also shown clinical efficacy in patients with the Muckle-Wells syndrome.

Studies with neurologic endpoints have shown marked improvement in symptoms, including opening pressure of the CSF on lumbar puncture (usually high in CAPS), papilledema, and MRI finding of inflammation. A more recent study found reversal of hearing loss in approximately one-third of patients with Muckle-Wells syndrome, although hearing loss was minimal in the study participants.

Anakinra dosing usually starts at 1 mg/kg and can be increased up to 6 mg/kg if efficacy decreases. Up to 200 mg can be administered in a single injection.

**Rilonacept**
This is an FDA-approved biologic for treating the CAPS autoinflammatory syndromes FCAS and Muckle-Wells; rilonacept has not been studied in patients with NOMID/CINCA. In clinical trials, it produced marked improvements in symptoms, including fever, rash, and pain.
The most commonly reported side effects associated with rilonacept use are injection-site reactions and upper respiratory tract infections.

The loading dose for rilonacept is 4.4 mg/kg, up to a maximum of 320 mg. Once-weekly dosing is 2.2 mg/kg, up to a maximum of 160 mg.

**Canakinumab**
This anti-IL-1 antibody has recently been approved by the FDA for MWS and FCAS and is being studied for NOMID. It is long acting so a dose of 2 mg/kg (max 150 mg/dose) can last for weeks, possibly months. In an open-label trial, it induced long-lasting remission for a mean of 104 days.9

**In this patient, which of the following symptoms is LEAST likely to respond to anakinra therapy?**

- a. Fever
- b. Rash
- c. Hearing loss
- d. Headaches
- e. Serum amyloid A levels

c. Correct.

**Case Continued**
Treatment with anakinra was initiated and the response was extremely good. Her fever, rash, and headache symptoms all improved. Her hearing loss continued, however, reflecting the extreme difficulty in reversing existing damage.

Although the patient responded well to anakinra, she complained of injection-site pain and was switched to rilonacept.

**Case 2**

**History / Physical Examination**

**Presenting Patient**

This patient is a 12-year-old male with an 8-year history of recurrent fever, severe abdominal pain, diarrhea, swelling around the eyes, muscle pain, and a rash that migrated from the proximal thigh toward the foot. Episodes last 1 to 3 weeks and occur every 2 to 3 months. Laboratory tests during and between episodes show markedly increased inflammatory indices. Family history revealed a sister with renal failure caused by amyloidosis.
Based on this clinical scenario, which protein mutation is indicated?

a. Mevalonate kinase  
b. TNF receptor  
c. Pyrin  
d. Cryopyrin  
e. Proline-serine-threonine phosphatase interacting protein 1

b. Correct.

**Natural History**

This case is a classic description of the TNF-α receptor-associated periodic syndrome (TRAPS). This disease can occur at any age but most cases occur during childhood. The median onset is 3 years of age, with three-fourths of cases occurring before age 10. However, of the genetic autoinflammatory syndromes, TRAPS is the most likely to start in adulthood. Thus, in an adult patient presenting with new onset of symptoms similar to this patient’s symptoms, TRAPS must be considered.

TRAPS is characterized mainly by recurrent fever episodes that typically last 1 to 4 weeks and occur 2 to 6 times per year. Patients usually have significant serositis, including chest pain and abdominal pain. Periorbital edema is a characteristic and fairly specific finding for this autoinflammatory condition. Patients often develop a painful migratory rash that usually starts in the trunk and migrates distally to the limbs over a course of a few days to several weeks. Severe myalgia can occur. Creatine phosphokinase levels are usually normal. Biopsies show fasciitis or panniculitis rather than myositis. Other symptoms may include arthritis or arthralgia. Many patients later develop amyloidosis.

This syndrome is caused by a mutation in the TNF 55 kDa receptor. More severe cases are structural mutations in the cystein protein, but a high prevalence of mutations are found in the more mild phenotypes. These “mild” mutations also may represent polymorphisms without clinical significance in normal persons.
Treatment

In the past, therapy was largely based on symptom relief. Most TRAPS episodes do not respond well to NSAIDS but are often responsive to steroids. In this patient, corticosteroid therapy was initiated after an unsuccessful trial of NSAIDS. However, she needed higher doses of steroids for longer periods, and over time, significant attacks reoccurred, highlighted by abdominal pain, diarrhea, and low-grade fever.

What would be the next therapeutic agent indicated?

a. Etanercept
b. Infliximab
c. Anakinra
d. Rituximab
e. Abatacept

a. Correct.

Early studies of TRAPS found that when TNF receptors were stimulated, there was decreased shedding of membrane-bound TNF, allowing unopposed TNF in the circulation. These findings appear to indicate that etanercept would be an ideal therapeutic agent to correct the shedding defect; however, clinical experiences have found that it wears off or fails.10-13

Even in cases that respond to therapy, inflammatory markers remain elevated. New knowledge has found TRAPS has a more complicated pathogenesis.
Etanercept was initiated at 0.8 mg/kg/wk. The dose was increased due to continued attacks and increased inflammatory markers to 1.2 mg/wk administered in three doses. After an initial response, the patient's disease stopped responding to etanercept.

What is the next therapeutic option?

a. **Infliximab**
b. **Adalimumab**
c. **Anakinra**
d. **Rituximab**
e. **Abatacept**

c. Correct.
Because this is an autoinflammatory disease, and IL-1 has an important role in inflammation, anakinra would be the best choice. Case reports have reported efficacy with anakinra in patients with TRAPS, including patients whose disease failed to respond to etanercept. Anakinra can be administered either continuously or at the beginning of an attack. Infliximab may worsen the disease because of a paradoxical decrease in apoptosis seen in infliximab-treated PBMC in patients with TRAPS. Clinical experience has shown that the anti-TNF antibodies (infliximab and adalimumab) may worsen the disease. In general, biologic therapies are only warranted in patients with cysteine mutations, frequent severe episodes that significantly impair their quality of life, or a family history of amyloidosis.

**Summary**

Interleukin-1β is known to play a major role in the autoinflammatory syndrome, so it makes sense that IL-1 therapy works for many patients. However, the pathogenesis is complex, and some intuitive assumptions, such as the effectiveness of TNF-receptor therapy for TRAPS, appear to be too simplistic.

Anti-IL-1 therapy has shown efficacy, particularly in the cryopyrin diseases. Three anti-IL-1 therapies are marketed (anakinra, rilonacept, and canakinumab) and others are being developed. However, therapies are less effective on some existing disease symptoms that represent disease-related damage, emphasizing the importance of early diagnosis and treatment.

Anti-TNF therapy may be effective for the chronic arthropathy related to some autoinflammatory syndromes, but they may be less effective in treating systemic symptoms and the inflammation itself.
References


