Cryopyrin-associated Periodic Syndromes: Discussion of Four Cases due to *NLRP3* Gene Mutations

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ABSTRACT

Cryopyrin-associated periodic syndromes (CAPS) are rare conditions that share a common etiology caused by various mutations in the *NLRP3* gene. *NLRP3* stands for NOD-like receptor (NLR) family, pyrin domain containing 3. These conditions entail three main autoinflammatory disorders: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID). These entities are diseases of the innate immune system, and their symptom complexes frequently overlap. They have a complex pathophysiology as well as clinical presentation with multiple organ system involvement and prominent skin findings. We present the cases of four patients with different CAPS: a father and his daughter with FCAS, a male patient with MWS, and a female patient diagnosed with NOMID at six years old. These cases underscore the importance of recognizing CAPS and the associated unusual constellations of symptoms in order to promote early intervention. Although these disease entities are rare, the genetic etiology makes them especially relevant when encountering related individuals with rheumatologic disease and/or urticarial skin lesions.

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INTRODUCTION

Cryopyrin-associated periodic syndromes (CAPS) are autosomal dominant autoinflammatory conditions due to a gain-of-function mutation in the *NLRP3* gene (although NOMID can be caused by other gene mutations and is often due to *de novo* mutations), which encodes the protein cryopyrin.[1,2] CAPS lack a clear antigen-antibody interaction in their pathophysiology, instead causing disease through a substance of the innate immune system known as cryopyrin. Cryopyrin instigates the generation of inflammasomes which are protein complexes that stimulate the production of Interleukin-1 beta (IL-1 beta). This interleukin production amplifies the inflammatory response, resulting in multisystemic symptoms.[1] Thus, the CAPS entail a spectrum of three rare autoinflammatory disorders: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID).[1]

The prevalence of CAPS is estimated to be 1 in 360,000 individuals in the United States. Due to the late recognition of these diseases and many instances in which the disease remains undiagnosed, actual prevalence may be greater.[3] CAPS often present with an assortment of rheumatologic and dermatologic findings that might prompt immediate referral to specialists in these two areas without a presumptive diagnosis. The phenotypes often vary and overlap with each syndrome. We seek to outline some of the patterns of those findings through a series of cases. We hereby present the cases of four patients with CAPS in order to prompt early recognition and to allow proper evaluation and treatment.

Muckle-Wells Syndrome

Patient 1

A 47-year-old Caucasian male with a past medical history of X-linked ichthyosis vulgaris presented to an outpatient family medicine clinic complaining of periodic "attacks" of diffuse redness of his skin and subsequent itching. These attacks were associated with joint pain, arthralgia, joint swelling, and pain localized to the long bones. There were no associated fevers; however, he did feel diffusely warm due to the significant erythema. These attacks typically lasted one to two hours at most; however, he did have chronic pain in his joints between attacks as well. He did not have any tongue swelling, lip swelling, or abdominal pain, but review of systems did reveal partial deafness in the right ear. He had taken prednisone, topical corticosteroids, indomethacin, and aspirin without relief. He did not recall being on colchicine, dapsone, or hydroxychloroquine. He denied a personal or family history of amyloidosis, early deafness, or renal disease. He had 3 cousins with ichthyosis vulgaris; he reported that his family has a history of X-linked ichthyosis and Muckle-Wells syndrome. On physical examination the patient had full range of motion of all the joints without any evidence of synovitis or joint effusion; however, he did have mild erythema over the metacarpophalangeal (MCP) joints and proximal interphalangeal (PIP) joints and pain on palpation of the PIP and MCP joints. Lower extremity examination revealed full range of motion in all joints without evidence of synovitis or joint effusion. His skin examination was remarkable for ichthyosis on the arms, legs, chest, and back, as well as longitudinal ridges in the nail beds. Neurologic exam was remarkable for decreased hearing on the right. He was diagnosed with Muckle-Wells syndrome.

Neonatal-onset multisystem inflammatory disease

Patient 2

A 34-year-old Caucasian female presented with a long history of a severe inflammatory syndrome that began at age 6. It prominently involved her joints with intermittent swelling of the knees and ankles as well as pain in her lower back in the sacroiliac areas. She also had episodes of severe headaches and acute onset extreme hip and groin pain leading to an inability to ambulate. These symptoms led to several hospitalizations. On review of symptoms she had no other complaints. Her medical history was notable for periodic fever syndrome of uncertain etiology, severe chronic headaches/migraines, idiopathic intracranial hypertension with ventriculoperitoneal shunt placement, a subdural hematoma responsive to burr hole surgery, chronic hearing loss requiring cochlear implantation in the left ear, positive antinuclear antibodies, and irritable bowel syndrome. There was no significant family history of fever or rheumatologic or dermatologic disease. Her medications included zonisamide, valproic acid, gabapentin, and anakinra. Physical exam was remarkable for papilledema and hearing

loss with resulting speech dysfunction. She had an unremarkable joint and skin exam. Several lumbar punctures showed significant meningeal irritation and inflammation without evidence of infection. She was diagnosed with neonatal-onset multisystem inflammatory disease and put on an experimental protocol using thalidomide as an immunosuppressant. Anakinra was replaced with canakinumab to improve her symptoms.

Familial Cold Autoinflammatory Syndrome (FCAS)

Patient 3

A 17-year-old Caucasian female presented with a history of unusual fever syndrome attacks beginning at the age of 3 months. She had daily attacks that presented with skin swelling and high fevers up to 103 degrees Fahrenheit. She occasionally missed school and could not function in her daily activities. She had no energy during these attacks and her feet and hands were sore and swollen. Her medical history was notable for a bicornuate uterus, dysmenorrhea, and panic disorder. Her only medications were ranitidine, cetirizine, and oral contraceptives. She had a family history of FCAS in her father. Genetic testing confirmed a diagnosis of FCAS. Canakinumab therapy was attempted. It was discontinued secondary to development of a painless rash on the calves, and replaced with anakinra. At 10-year follow-up, she reported her son had been diagnosed with FCAS and was under management with canakinumab.

Patient 4

A 66-year-old Caucasian male presented with a reported life-long history of daily fevers, especially with cold exposure. He also developed diffuse hives all over his body followed by general stiffness and chills during these episodes, which were also accompanied by diffuse achiness of the knees and ankles that improved overnight. Review of systems was noncontributory. His medical history was notable for benign prostatic hypertrophy, a broken ankle, and 2 episodes of nephrolithiasis. His family history was significant for amyloidosis in his mother, a daughter with FCAS, and a cousin with cold urticarial fevers and renal insufficiency. His medications included ranitidine, naproxen, and anakinra. Genetic testing done confirmed FCAS in this patient and many family members.

DISCUSSION

Cryoprin-Associated Periodic Syndromes (CAPS) encompass three diseases related to a defect in a single gene known as *NLRP3*. These diseases include familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal onset multisystem inflammatory disease (NOMID). As demonstrated in three of the four patients presented above, these disorders are inherited in an autosomal dominant pattern with variable penetrance.[4] Cases like NOMID are more commonly attributed to *de novo* mutations due to the severity of the disease making reproduction unlikely. The pathophysiology of CAPS has been elucidated to a certain extent and is demonstrated in Figure 1.

The *NLRP3* gene encodes a protein known as cryoprin. Cryoprins are proteins of the innate immune system that normally function to help form inflammatory complexes that react to intracellular pathogens.[5] The mutant protein in these diseases is theorized to inappropriately form inflammatory complexes called inflammasomes which then aggressively produce IL-1 beta and other inflammatory cytokines by cleaving their inactive precursors. These surges of inflammatory cytokines cause the systemic effects of these diseases.[1,6]

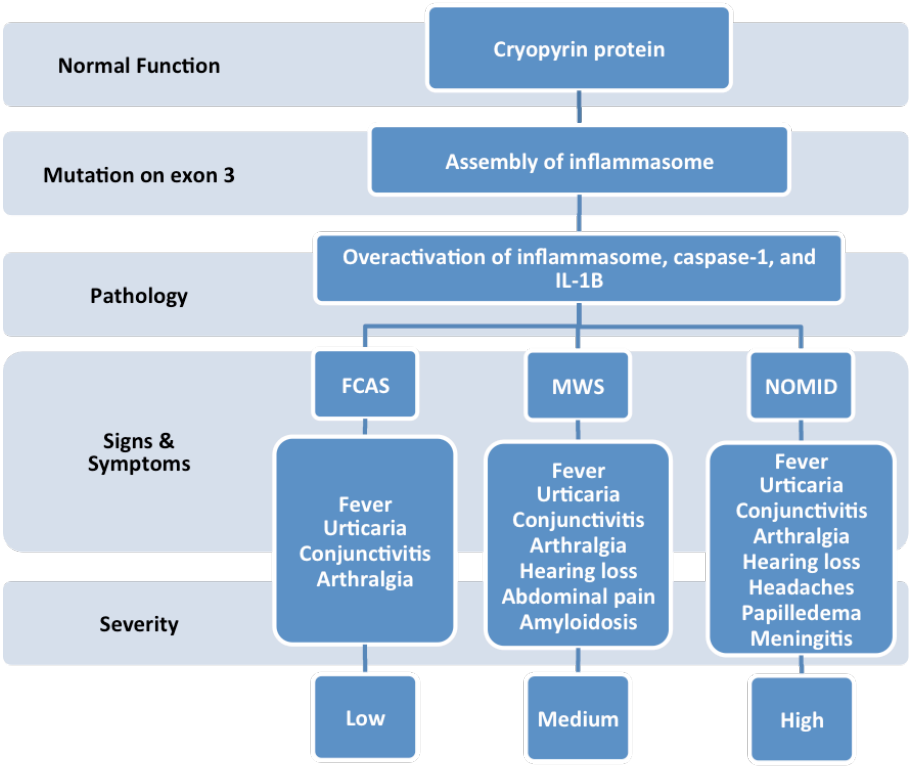

Figure 1. Pathological mechanism underlying autoinflammatory syndrome involving gene mutations.

Symptoms of CAPS typically include headache, fatigue, eye disorders, rash, fever, hearing loss, central nervous system dysfunction, and musculoskeletal disorders.[3] Other sequelae include arthritis, rash, conjunctivitis, sensorineural deafness, meningitis, and intellectual disabilities.[7]

An important feature in the family history of one of our patients was the development of renal failure. Approximately 25% of CAPS patients experience systemic amyloidosis leading to renal failure within a 5-10 year time frame.[7-9] Additionally, the presence of urticaria shared by patient 4 and his family is fairly common and characteristic of autoinflammatory disorders.

The diagnosis of CAPS is usually made using information from the clinical presentation in conjunction with genetic testing,[3] however the genetic test may be normal. False negative results are more common in MWS and NOMID. In the case of our four patients, a diagnosis was made based primarily on the constellation of symptoms. One analysis of greater than 800 samples sent for *NLRP3* gene testing revealed that a positive result was unlikely unless the patient had at least 3 episodes of recurrence, presented at less than 20 years of age, and had elevation of C-reactive protein. Therefore, the presence or absence of these characteristics should be considered prior to undergoing expensive gene testing.

Drug therapies are based on the common target of IL-1 beta overproduction in these disorders. Treatment modalities vary among the syndromes and include anakinra, rilonacept, and canakinumab. Since these three disorders involve a mutation in the *NLRP3* gene, which regulates IL-1, the blockade of IL-1 is a common therapeutic option for all three conditions.[7,11-13] Canakinumab, a monoclonal antibody targeted against IL-1beta, has been reported to have great efficacy with remission of symptoms in CAPS

patients.[3,7] However, canakinumab can lead to intolerable dermatologic symptoms, as demonstrated by the rash patient 3 developed.

FCAS presents in early childhood, sometimes at birth, and is a lifelong condition as demonstrated in patients 3 and 4. FCAS is an extremely rare condition with an occurrence of less than 1 case per million individuals. The autosomal dominant pattern of inheritance is evident in our patient's case since the father and daughter both had the disease. Importantly, a majority of the family members had cold urticaria. This leads us to hypothesize that the urticaria may have been misdiagnosed in the family and that the family members actually suffered from FCAS. The case presents a significant history of family members with this rare disorder. The debilitating nature of FCAS is evidenced by the fact that the patient 3 could not function in daily activities and experienced difficulty with attending school.

Muckle-Wells syndrome (MWS) is an autoinflammatory disease.[14] In comparison to the other cryopyrin-associated periodic syndromes like FCAS and NOMID, MWS is a milder disease form.[15] A major challenge in MWS is that there are no clinical criteria that can help a clinician arrive at a diagnosis.[15] Kuemmerle-Deschner et al.[15] have proposed three distinct phenotypes of MWS: an inflammatory phenotype generally seen in childhood, an intermediate phenotype, and an organ-disease phenotype of adult age in which hearing loss is a hallmark (occurring in about half of all adult patients).

Our patient presented with complete deafness in the left ear and partial deafness in the right ear but with no fever. This is unusual as generally patients with MWS present with hearing loss and periodic fevers followed by a rash. Interestingly, our patient also had a history of icthyosis vulgaris. The literature does not report any association between icthyosis vulgaris and MWS.

NOMID is the most severe phenotypes of the CAPS syndromes.[16] A noteworthy aspect of our patient's presentation is that she presented with NOMID at age 6, compared to most patients with NOMID syndrome presenting at birth. Typical symptoms of NOMID include several eye problems including conjunctivitis, as well as optic disc atrophy and papillary edema due to increased intracranial pressure.[3] Our patient presented with papilledema and frequent headaches. Importantly, progressive sensorineural hearing impairment is also seen, as in MWS.[3] While our patient presented with hearing loss, she had no fevers. Patients with NOMID are unique compared to those with the other CAPS syndromes in that they do not typically experience fever. The disease is also unique in that it can be caused by mutations outside the *NLPR3* gene. Features that are exclusive to NOMID include skeletal abnormalities such as arthropathy and uncontrolled growth in the epiphysis of long bones and the patella.[17]

Cryopyrin-associated periodic syndromes are rare conditions secondary to *NLRP3* gene mutations. Familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and Neonatal-onset multisystem inflammatory disease (NOMID) syndrome represent overlapping disease processes sharing mutations in a common gene. While CAPS usually presents early in a patient's childhood, adults may show mild symptoms and go unrecognized. Thus, when encountering patients who present with cold urticaria and periodic fevers, it is important for clinicians to consider CAPS. Other symptoms to alert the physician include arthritis with these attacks, sensorineural hearing loss, and progressive renal impairment from amyloidosis in longstanding cases. Neonatal onset of urticarial skin rashes, skeletal abnormalities, sensorineural hearing loss, papilledema, and chronic meningitis among other unusual symptoms should lead one to suspect NOMID. It is

important to recognize that the age of presentation and disease symptoms may vary greatly as well, as seen with our NOMID patient who did not actually present in the neonatal period. Practitioners should have a working knowledge of how to recognize these unique presentations.

LEARNING POINTS

1. Familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and Neonatal-onset multisystem inflammatory disorder (NOMID) are related conditions along a spectrum of disease severity.

2. Clinical features common to FCAS, MWS, and NOMID include recurrent fever and urticaria, arthralgia, and conjunctivitis.

3. A delay in diagnosis, and therefore treatment, of cryopyrin-associated periodic syndromes can result in organ damage such as hearing loss and renal insufficiency due to amyloidosis.

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