A rare hereditary disease: Muckle-Wells syndrome

Nitya Ramreddy,¹ Aviva Hopkins,²,³ Carlos Lozada²
¹Department of Internal Medicine; ²Department of Rheumatology, University of Miami Miller School of Medicine, Miami; ³Holy Cross Hospital, Fort Lauderdale, FL, USA

Abstract

Cryopyrin associated periodic syndrome (CAPS) is a dominantly-inherited autoinflammatory disease, which is included in the group of periodic fever syndromes. It is caused by a defect in the regulation of inflammatory cytokines, particularly interleukin-1β. CAPS encompasses a spectrum of three phenotypes of increasing severity: familial cold autoinflammatory syndrome, Muckle-Wells syndrome (MWS) and neonatal onset multisystem inflammatory disease. We report the case of a 58-year-old male, who had migratory joint pains, daily urticaria, chills, and episodic conjunctivitis since childhood and hearing loss in his 20s with a family history of similar symptoms. He was diagnosed with MWS after being found to have a R262W gene mutation in NLRP3 gene and successfully treated with canakinumab. After his discovery, other 1st and 2nd degree family members with similar complaints were found to have the same genetic mutation and were also successfully treated with canakinumab.

Introduction

Cryopyrin associated periodic syndromes (CAPS) are rare, dominantly-inherited autoinflammatory diseases characterized by recurrent episodes of systemic inflammation involving multiple tissues including joints, skin, the central nervous system, eyes, and ears. Unlike autoimmune diseases, CAPS are related to dysfunction of the innate immune system. The syndromes are due to dominant mutations in NLRP3, which encodes a key component of the innate immunity that regulates the secretion of interleukin-1 (IL-1β). There is a spectrum of three phenotypes, sometimes clinically overlapping, of increasing severity: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and neonatal onset multisystem inflammatory disease (NOMID). MWS has an intermediate phenotype of severity characterized by intermittent episodes of fever, urticarial rash, joint pain, progressive hearing loss, and, sometimes, secondary amyloidosis with nephropathy.

Case Report

A 58-year-old male with past medical history of hearing loss at age of 23 while serving in the military working with aircraft, presented to the office complaining of fatigue and right wrist pain and swelling. He reported years of migratory joint pains and swelling, the first episode of which occurred at age 19. He had since experienced different joint pains with and without accompanying joint swelling on an almost weekly basis. Review of systems was notable for fatigue, frequent headaches and a daily rash. The patient described daily episodes of non-pruritic, painful, erythematous spots all over his body since childhood. Rash was worse in the evenings, associated with chills, and not aggravated by exposure to cold. After being noted to have conjunctival injection, with further questioning, patient reported that he had experienced intermittent eye redness since his time in the military, which he attributed to a presumed chemical exposure. He denied fevers, myalgias, chest pain or shortness of breath. No history of recent vaccinations or travel. He endorsed drinking alcohol occasionally but never smoked cigarettes or used any illicit drugs. Family history was notable for mother and sister with daily exposed hives since infancy has been unable to afford treatment because of insurance issues.

Correspondence: Nitya Ramreddy, Department of Internal Medicine, University of Miami Miller School of Medicine/Holy Cross Hospital, Federal Hwy, Fort Lauderdale, FL 33308, USA. Tel.: +1.312.613.5131. E-mail: nr49@med.miami.edu

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Discussion and Conclusions

CAPS are a group of rare hereditary disorders that includes three phenotypes: FCAS, MWS and NOMID.¹ Drs. Muckle and Wells first described an autosomal dominant syndrome in 1962 manifested as urticaria, chills, sensorineural hearing loss, and renal amyloidosis, which came to be known as MWS.² CAPS occur due to a missense mutation in the NLRP3 gene located on chromosome 1q44, which codes for cryopyrin.³ Cryopyrin helps inflammasomes cleave IL-1β. The defect in cryopyrin leads to elevation of interleukins with resultant inflammatory symptoms such as urticaria and arthralgia.⁴ Diagonsis is usually made by skin
biopsy which shows perivascular and neutrophilic dermal infiltration and/or genetic testing in an individual with suggestive symptomatology. Genetic testing will often demonstrate a mutation in NLRP3 gene, mostly in exon 3. IL-1 inhibitors have been shown to be effective in the treatment of CAPS and include Anakinra, Rilonacept and Canakinumab. Anakinra is an IL-1 antagonist, which binds to IL-1 receptor and blocks its activity. It is given as a daily subcutaneous injection and leads to symptom remission. Rilonacept also binds to IL-1 type 1 receptor and is given as a weekly injection. Canakinumab is a human IgG1 anti-IL-1b monoclonal antibody, with a half-life of 26 days. It is generally administered as a subcutaneous injection every 8 weeks, but the frequency of canakinumab dosing can be dependent on the phenotype and severity of the disease. A multi center study conducted to determine the efficacy of Canakinumab in patients with CAPS showed that the real life effectiveness is lower than expected and treat to target strategy improves outcomes in patients. Our patient achieved complete resolution of symptoms within 2 days following his first dose of canakinumab. After he had continued remission following his second dose 8 weeks later, he decided to see how long he could go without symptom recurrence. He elected to receive his third dose 6 months later when fatigue began to return, leukocytosis worsened, and inflammatory markers increased. Following that injection, he opted for his next dose at 4 months because of again slight recurrence of fatigue. Currently, he has not had a headache, joint pain, eye redness or urticarial rash since the first injection. CAPS are rare hereditary diseases and the diagnosis is often delayed. However once the diagnosis is confirmed, there are very effective, life-altering treatments.

References