CASE REPORT

Rare but revealing: The first report of familial CAPS in Saudi Arabia

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ABSTRACT

Background and aim: Cryopyrin-associated periodic syndrome (CAPS) is a rare autosomal dominant autoinflammatory disease caused by mutations in the NLRP3 gene, leading to interleukin-1β overproduction and systemic inflammation. It is subcategorized into familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), or neonatal-onset multisystem inflammatory disease (NOMID). To the best of our knowledge, this is the first reported familial CAPS in Saudi Arabia. A 28-year-old Saudi male with a lifelong history of recurrent urticaria, polyarthritis, and systemic complaints underwent clinical evaluation, laboratory testing, imaging, and genetic analysis. Family history was reviewed to assess possible hereditary involvement.

Results: The patient presented with cold-induced urticaria, inflammatory polyarthritis, chronic sacroiliitis, migraines, tinnitus, and gastrointestinal symptoms. Autoimmune serologies were negative, but C-reactive protein was elevated. MRI revealed bilateral sacroiliitis. Genetic testing identified a pathogenic heterozygous NLRP3 mutation, confirming autosomal dominant CAPS, FCAS subtype. Several relatives reported similar cold-induced symptoms, indicating a familial pattern. This represents the first documented familial CAPS case in Saudi Arabia.

Conclusion: CAPS is frequently underdiagnosed due to overlapping features with more common rheumatologic and dermatologic conditions. This case underscores the importance of early recognition, genetic confirmation, and family screening. Prompt initiation of IL-1–targeted therapy is critical to prevent complications and improve quality of life. Increasing clinician awareness is essential, particularly in regions where CAPS has not been previously reported. (www.actabiomedica.it)

Key words: cryopyrin-associated periodic syndrome, CAPS, familial cold autoinflammatory syndrome, NLRP3 mutation, autoinflammatory disease, case report

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Introduction

Cryopyrin-associated periodic syndrome (CAPS) is a rare and hereditary disease caused by mutation in NLRP3 gene, which is associated with increased expression interleukin (IL)-1β and systemic inflammation. It has three phenotypes according to severity: Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS), and Neonatal-Onset Multisystem Inflammatory Disease (NOMID) (1). A diagnostic model has been developed based on elevated inflammatory markers (C-reactive protein or serum amyloid A) and presence of at least two out of six hallmark CAPS symptoms: urticaria-like rash, cold-induced attacks, sensorineural hearing loss, musculoskeletal complaints, chronic aseptic meningitis, and skeletal abnormalities. The sensitivity of this model was revealed to be 81% and specificity of 94% (2). FCAS is the mildest form and it is inherited in autosomal dominant pattern. Patients commonly have symptoms such as rash, joint pain, headache, and chills upon exposure to cold temperatures. MWS symptoms includes migraines, hearing loss, and joint pain. In later stages, it can lead to the accumulation of amyloidosis and kidney damage. The most severe form is NOMID, a lifelong disease that presents in early childhood. It combines symptoms from both FCAS and MWS along with aseptic meningitis, bony deformities, developmental delay, and significantly reduced life expectancy (3,4). The prevalence of CAPS is estimated between 1 to 3 cases per 1 million children and adults globally (5). Thus far, no reported cases of familial CAPS in Saudi Arabia. This is the first documented case of Familial CAPS in Saudi Arabia. In this case, symptoms were nonspecific and were initially mistaken with more common condition, contributing to delayed diagnosis. The diagnosis was eventually made after paying attention to pattern of symptoms and family history along with further investigation.

Case report

This is a case of a 28-year-old Saudi male, height 167cm, weight 81 kg, presented with recurrent urticaria and polyarthritis since the age of two. The urticarial wheals are itchy and heals with no scarring, provoked by cold weather and humidity. There is no angioedema and it is currently partially controlled with anti-histamine (fexofenadine). The involved joints are mostly hands, wrists and lower limbs, with morning stiffness lasting for more than one hour. The pain was on and off, but recently became permanent. He also reported chronic lower back and neck pain with stiffness and radiation to both lower limbs. Systemic symptoms include migraines for two years, not improved with NSAIDS, blurry vision (without vision loss), dry eyes, and recurrent ear pain with tinnitus. Also, he had gastrointestinal issues such as alternating diarrhea and constipation with bloating and two episodes of rectal bleeding in one year. Colonoscopy was unremarkable except for small hemorrhoids. On physical examination, there was urticarial wheals scattered over the body without angioedema. Joint examination showed synovitis at MCPs, PIPs, and wrists, neck and spine stiffness with bilateral positive FABER test. The ice cube test was negative, making cold-induced urticaria less likely. Early workup revealed a seronegative inflammatory arthritis, negative rheumatoid factor, anti-CCP, ANA, and Anti-dsDNA antibodies. ESR is normal, but CRP is elevated 25mg/L (normal <5 mg/dL). MRI imaging of the sacroiliac joints showed chronic bilateral sacroiliitis. Since the disease started at an early age, involved multiple systems, flared with cold exposure, and had a familial pattern, genetic testing was done. It identified a pathogenic heterozygous mutation in NLRP3 gene, therefore, autosomal dominant Cryopyrin-Associated Periodic Syndrome (CAPS) was diagnosed. There is a history of consanguinity between the patient's parents; however, there are not first degree relatives. Interestingly, upon further history taking, there was multiple family members affected (Figure 1). The patient has four brothers and one sister; among them, one brother and the sister had recurrent urticaria and transient fevers, which are now under investigations to rule out CAPS. In addition, his mother has three sisters and three brothers, The mother, two sisters and two brothers reported similar presentation.

Discussion

Cryopyrin-associated periodic syndrome (CAPS) is a rare, inherited autoinflammatory disorder resulting

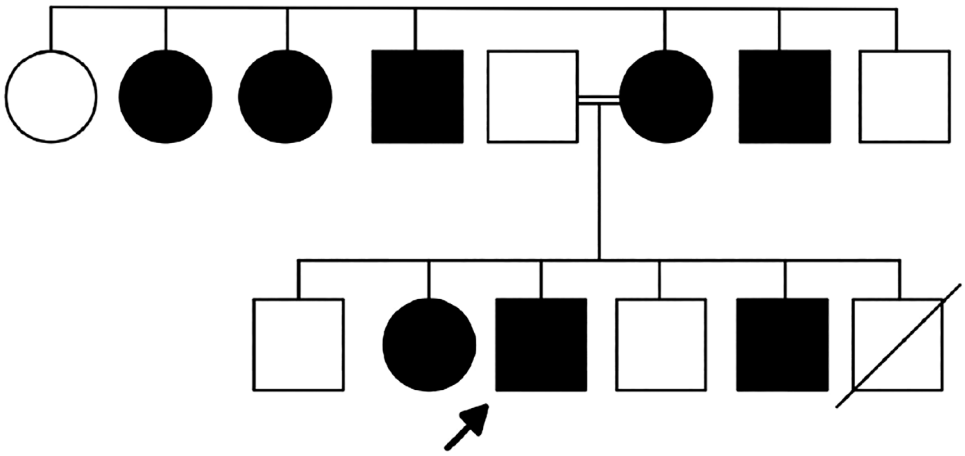

Figure 1. Pedigree of the patient's family.

from mutations in the NLRP3 gene, leading to overproduction of interleukin (IL)-1β and subsequent systemic inflammation (1). Clinically, CAPS presents in three phenotypes with varying severity: Familial Cold Autoinflammatory Syndrome (FCAS), being the mildest form, Muckle-Wells Syndrome (MWS), and the most severe form is Neonatal-Onset Multisystem Inflammatory Disease (NOMID) (1). A diagnostic criteria with sensitivity of 81% and a specificity of 94% has been established based on elevated inflammatory markers, such as C-reactive protein (CRP) or serum amyloid A, in addition to at least two out of six clinical features: 1. urticaria-like rash, 2. cold-induced flares, 3. sensorineural hearing loss, 4. musculoskeletal symptoms, 5. chronic aseptic meningitis, and 6. skeletal abnormalities (2). Our patient meets these diagnostic criteria, as he presents with cold-induced urticaria and musculoskeletal pain, along with elevated CRP. The prevalence of CAPS is estimated to be between 1 and 3 cases per million people worldwide (5). The clinical manifestations of CAPS may mimic more prevalent disorders, potentially leading to misdiagnosis; therefore, enhancing clinician awareness is critical for facilitating early identification and optimal management of the condition. Notably, our patient remained undiagnosed for 2 decades, which resulted in a significant delay in both diagnosis and initiation of appropriate treatment. To the best of our knowledge, this is the first reported familial CAPS in Saudi Arabia. FCAS, the mildest form, follows an autosomal dominant inheritance pattern and typically manifests as cold-induced rash, joint pain, headache, and chills. MWS presents with recurrent migraines, hearing loss, and arthralgia, and may progress to AA amyloidosis and renal dysfunction in advanced stages. NOMID is the most severe form, presenting in infancy with symptoms overlapping those of FCAS and MWS, in addition to aseptic meningitis, skeletal deformities, developmental delay, and significantly shortened life expectancy (3,4). Complications of CAPS are diverse and may involve multiple organ systems, particularly in patients with more severe phenotypes such as CINCA. Neurological involvement is among the most significant, with manifestations including chronic headaches, papilledema, seizures, and developmental delay. These symptoms may progress to long-term sequelae such as optic atrophy and sensorineural hearing loss, underscoring the importance of early neurological screening and long-term monitoring. Another major complication is AA amyloidosis, reported in up to 10% of cases, most commonly manifesting after the third decade of life. Elevated levels of serum AA have also been associated with infertility, especially in patients with MWS and CINCA subtypes. Although some reports describe pulmonary, cardiac, hepatic, and renal involvement in CAPS, the exact pathological mechanisms affecting these organs remain insufficiently defined. Overall, early recognition and management of these complications are essential to improving long-term outcomes and quality of life in affected individuals (6).

AA amyloidosis typically responds well to IL-1 inhibitors when detected at an early stage. According to the 2021 EULAR/American College of Rheumatology guidelines, achieving prompt disease control with IL-1 inhibitors is crucial to prevent irreversible organ damage, minimize adverse effects from inappropriate therapies, and improve both disease outcome and quality of life (7). In addition, screening family members who their symptoms have possibly been overlooked is essential part of the management plan. Although the effectiveness of biologic therapy in the management of CAPS is well established, data regarding its long-term efficacy remain limited. Common side effects of these agents includes headache, pyrexia, increased risk of bacterial infections, especially respiratory tract infections. Other rare side effects include vertigo and angle-closure glaucoma for canakinumab (6). Our patient had the FCAS form, which, to the best of our knowledge, represents the first reported case of this form in Saudi Arabia. As FCAS is the mildest phenotype of CAPS, patients may go years without an accurate diagnosis, resulting in delayed initiation of treatment. In this case, the patient is about to marry a second-degree relative and was therefore advised to undergo genetic testing prior to marriage. Had the diagnosis been established earlier, appropriate genetic counseling could have been provided, potentially preventing transmission of the disease to future offspring. Other cases of CAPS in Saudi Arabia were described by Alenazi et al., who reported autoinflammatory diseases in children at a rheumatology clinic, with two of the cases being MWS (8). In conclusion, this report highlights the significance of establishing a clinical diagnosis based on recognized diagnostic criteria, complemented by genetic confirmation. Owing to the rarity of CAPS, increasing awareness, early identification and prompt initiation of targeted biologic therapy are critical to preventing irreversible complications and optimizing long-term patient outcomes and quality of life.

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