

Correspondence and Replies

Cold-induced urticaria in a child with familial Mediterranean fever



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To the Editor:

We read the article “Acquired cold-induced urticaria in pediatric patients: A 22-year experience in a tertiary care center (1996-2017)” with great interest.¹ The authors reported the association of autoimmune diseases in 3.6% of their patients; however, there was no patient with cold-induced urticaria and autoinflammatory disease. We would like to share our experience with a patient who presented with typical attacks of familial Mediterranean fever (FMF) except for urticaria triggered by cold, occurring mostly during attacks.

A 12-year-old boy admitted to our hospital with recurrent attacks of fever, abdominal pain, chest pain, and urticarial rash. These attacks were present since he was 3 years old. He was compound heterozygous for M694V and R761H mutations on the *MEFV* gene. He had been using colchicine since he was 4 years with the diagnosis of FMF. The attack frequency significantly decreased with colchicine. With the clinical findings and genetic test results, FMF diagnosis was certain; however, urticaria during attacks was atypical for FMF. His mother explained that he had rash only in the locations where she applied cold cloths to reduce fever during attacks. He also had rash in attack-free periods with direct contact to cold water/objects and exposure to cool air. With this information, we suspected cold-induced urticaria and performed ice-cube challenge test (ICCT), the result for which was positive at 10 minutes. He did not have cough, dyspnea, or hypotension triggered by cold. We diagnosed cold-induced urticaria as an associated condition in this patient with FMF. This is the first report of such co-occurrence. Avoidance of cold exposure and use of nonsedating H1-antihistaminic drugs (on demand) were recommended to the patient.

FMF is an autosomal-recessive autoinflammatory disease characterized by recurrent attacks of fever and polyserositis caused by mutations in the *MEFV* gene.^{2,3} Rash is very rare during FMF attacks. The only cutaneous manifestation of FMF is erysipelas-like erythema, which mostly occurs around the ankles.⁴ Urticaria during attacks suggests diagnosis of other autoinflammatory diseases such as cryopyrin-associated periodic syndrome (CAPS).⁵ The patients with familial cold autoinflammatory syndrome (FCAS) (the disease at the mild end of the CAPS spectrum) experience attacks of fever and urticaria triggered by cold.⁶ It is important to note that the attacks are triggered by general cold exposure such as air-conditioned rooms or cool breezes in FCAS and not by direct contact with cold water or objects, which is the case in cold-induced urticaria.⁶ The ICCT result is negative in FCAS, whereas it is usually positive in cold-induced urticaria.⁷ Our patient was experiencing attacks of high fever, abdominal pain, and chest pain, which were typical for FMF, and cold cloth application to reduce fever triggered the cold-induced urticaria. If the details of the history had not been investigated, the differential diagnosis of autoinflammatory diseases would have been challenging in this patient, suggesting a diagnosis of CAPS rather than FMF. The detailed description of rash made us consider the correct diagnosis as co-occurrence of cold-induced urticaria and FMF in this patient, which was confirmed by the ICCT.

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Reply



To the Editor:

We thank Batu and Vezir for their comments¹ on our article.² We read their case report with great interest.

Interestingly, Nakamichi et al recently reported on a 75-year-old woman with recurrent cold urticaria and leg edema responsive to colchicine.³ The patient was found to have both a heterozygous mutation in *NLRP3* (p.Ala439Val) and a homozygous mutation in *MEFV* (p.Glu148Gln), which has been associated with autosomal-recessive familial Mediterranean fever (FMF).⁴

We are not aware of any patients followed in our program with cold-induced urticaria and FMF. Our study specifically excluded patients with known autoinflammatory disorders, to focus on acquired cold-induced urticaria not associated with familial cold inflammatory syndromes.

Four patients in our study did have clinically documented periodic/recurrent fevers (Table II).² Three of these patients were also evaluated by pediatric rheumatologists at our institution. All 3 had genetic testing performed for a panel of genes associated with periodic fever syndromes, and none received a clinical diagnosis of FMF. One patient was found to have a heterozygous variant in *MEFV* (c.1172T>C, p.Ile591Thr), which has been reported as both a benign polymorphism and potentially associated with FMF.⁵ This patient did not have a clinical diagnosis of FMF.

A second patient had a heterozygous variant in LPIN2 (c.991G>T, p. Ala331Ser). Majeed syndrome, a rare familial autoinflammatory syndrome characterized by early onset chronic recurrent multifocal osteomyelitis and neutrophilic dermatosis, is associated with autosomal-recessive mutations in LPIN2.⁶ However, this patient's mutation was heterozygous and has been reported as a benign variant.⁷ Panel testing for other genes associated with periodic fever, including *MEFV*, was otherwise negative in these 3 patients.

Although familial cold autoinflammatory syndromes and periodic fever syndromes such as FMF are rarer than acquired cold urticaria, the cases reported by Batu and Vezir and by Nakamichi et al illustrate the importance of ruling out auto-inflammatory conditions in subjects with cold-induced urticaria, to provide adequate therapy to these patients.

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Delabeling penicillin allergy: Is skin testing required at all?



We read with interest the article by Kleris et al,¹ highlighting the use of a dedicated penicillin skin test clinic to improve access

to testing in adult patients. Of 104 evaluated for penicillin allergy, 95 (91.3%) had negative skin testing and passed an oral challenge. Although the 4 patients with positive intradermal testing were not challenged, none had a history of anaphylaxis, and the majority of patients overall (84.5%) reported reactions occurring more than 10 years before testing.

It has been well established that rates of penicillin allergy decrease over time with the majority of patients outgrowing their allergy within 10 years after diagnosis.² Skin prick testing has risks of false-positive results. In fact, in a recent study of 25 adult patients with positive skin testing to penicillin, only 9 (36%) reacted on a graded oral challenge.³ In addition, studies have also supported the safety and efficacy of a graded oral challenge alone in ruling out beta-lactam allergy. A recent study by Mill et al⁴ of 818 children labeled as amoxicillin allergic noted that a graded oral challenge was established to have a specificity of 100% (95% confidence interval [CI], 90.9% to 100.0%) with a negative predictive value of 89.1% (95% CI, 77.1% to 95.5%) and a positive predictive value of 100.0% (95% CI, 86.3% to 100.0%). Furthermore, it was noted in the same paper that the sensitivity of a skin test for the diagnosis of amoxicillin allergy is less than 10%.⁴ As most patients labeled as beta-lactam allergic are, in fact, not allergic, one could argue that skin testing clinics are not required at all. Perhaps access to evaluation of penicillin allergy is better accomplished with dedicated graded oral challenge clinics targeting low-risk cases (eg, those who experienced mild symptoms limited to the skin). This limitation was not addressed by the authors.

Moving forward, the authors agree that evaluation of penicillin allergy is paramount as being labeled allergic has significant consequences including increased antibiotic resistance, longer hospital stays, and higher morbidity.⁵ However, we argue that the way forward is with a graded oral challenge for low-risk cases, as opposed to dedicated skin prick testing clinics.

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