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Post COVID recurrent fever in children with polymorphisms in the innate immunity regulator, pyrin; *MEFV* gene

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Clinical Implications

Children with persistent recurrent fevers after coronavirus disease 2019 (COVID-19) infection should be tested for polymorphisms in the innate immunity regulator, pyrin; gene *MEFV*. These children improve with daily colchicine therapy.

Emerging after the global transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), reports of prolonged symptoms after coronavirus disease 2019 (COVID-19) illnesses were reported. Now known as long-COVID or post-COVID by the U.S. Centers for Disease Control and Prevention, they are defined as persistent symptoms lasting longer than 12 weeks after the initial illness. A meta-analysis of pediatric patients observed 25% of pediatric patients experiencing long-COVID symptoms. Approximately 2% of these patients experienced recurrent fever.[1] We present 2 adolescent males with a pathogenic heterozygous mutation in the innate immunity regulator, pyrin: *MEFV* gene (p. A744S) in the setting of recurrent fever, fatigue, and brain fog after SARS-CoV-2 infection. Treatment with colchicine significantly improved these symptoms.

The first patient was a 13-year-old unimmunized male who experienced COVID-19 illness in January 2022. Prior to his illness, his mother reported intermittent flushing with a maximum temperature of (99°F [37.2°C]) occurring every 2 to 3 weeks. When he was evaluated in March 2022, he was experiencing recurrent fever (101°F [38.3°C]), arthralgias, fatigue, and brain fog that coincided with fevers. Symptoms would last for 1 to 2 days and recur every 4 to 5 days. Pharyngitis, aphthous ulcers, and adenopathy were absent. His medical history was notable for attention deficit disorder, and his family history was positive for atopy and migraine headaches. His family's heritage was European. No other family members endorsed recurrent fevers despite having also contracted COVID-19.

The second patient was a 10-year-old, fully immunized, male who also had acute COVID-19 in January 2022. He was evaluated in June 2022 and had symptoms of fevers (101°F [38.3°C]), brain fog, fatigue, pharyngitis, and disequilibrium occurring every 3 to 4 days. Aphthous ulcers or adenopathy was not reported. His mother reported a history prior to COVID-19 infection of recurrent fevers (101°F [38.3°C]) every 6 to 8 days. He had previously been evaluated for recurrent fevers, but no infectious, malignant, or autoimmune trigger had been identified. The child's family was of European (Spanish and Irish) heritage with a family history positive for autoimmunity and atopic disease.

Both patients underwent laboratory analysis for inflammatory markers and cytokine analysis (Table I) at the time they were afebrile. Erythrocyte sedimentation rate and ferritin levels were elevated in the second patient only and plasma T-helper (Th1 and Th2) cytokines (by Luminex) were all within normal limits. These patient's recurrent fever history prompted genetic testing (Invitae autoinflammatory panel) that identified a heterozygous, pathogenic mutation in the *MEFV* gene (p. A744S) that encodes pyrin; a protein that regulates inflammasome activation in response to infection. In both patients, this variant was inherited from the mother. The second patient's brother (age 14 years) carried the same mutation but was not symptomatic despite experiencing COVID-19 concurrently (Figure 1). Colchicine therapy (0.6 mg twice daily) was initiated for both patients resulting in near-immediate resolution of fevers and improvement in other symptoms. They were also evaluated by a pediatric rheumatologist who agreed with a trial of colchicine and suggested familial Mediterranean fever (FMF) in the first patient and PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and adenitis) in the second, although both had atypical presentations.

TABLE I. Cytokine and inflammatory marker analysis*

Cytokine	Normal Range	Patient 1	Patient 2
TNF-α	0–22.30 pg/mL	7.65	6.37
IFN-γ	0–24.10 pg/mL	<3.20	<3.20
IL-10	0–19.00 pg/mL	6.55	<3.20
IL-6	0–11.90 pg/mL	4.44	<3.20
IL-2	0–60.80 pg/mL	<3.20	<3.20
IL-4	0–4.10 pg/mL	<3.20	<3.20
IL-5	0–4.10 pg/mL	<3.20	<3.20
IL-12	0–8.40 pg/mL	<3.20	<3.20
Patient 1	ESR	Ferritin	Temperature (°C)
February 15, 2022	8	26.8	36.2
September 8, 2022	8	28	36.5
Patient 2	ESR	Ferritin	Temperature (°C)
March 11, 2022	29	94	37.9
May 23, 2022	21.9	103	37.2

ESR, Erythrocyte sedimentation rate; *IFN-γ,* interferon gamma; *IL,* interleukin; *TNF-α,* tumor necrosis factor alpha.
*Values were obtained when the patients were afebrile.

Periodic fever syndromes including PFAPA and FMF usually begin in early childhood with PFAPA typically remitting in childhood and FMF persisting lifelong. The PFAPA is the most common periodic fever syndrome in children and is polygenetic. One study found the heterozygote A744S *MEFV* variant in 10% of patients with PFAPA.[2] The FMF is a monogenetic disease characterized by episodes of pleuritis, arthritis, gastrointestinal symptoms, or rash with accompanying fever. Mutations in *MEFV* have been identified in approximately 5% of patients with European ancestry in the United States with higher prevalence in the Middle East.[3] Of these populations, only 1% to 2% of patients develop clinical symptoms suggesting incomplete penetrance and/or genetic or environmental cofactors.[3,4] In both PFAPA and FMF, treatment with colchicine is effective, likely through disruption in microtubule trafficking of inflammasome-related proteins, thereby, reducing overall inflammasome production.[5,6]

FIGURE 1. Pedigrees for patient 1 and patient 2.

A recent study reported worsening FMF symptoms after acute COVID-19 illness in 33% of patients with FMF,[7] perhaps through additive inflammasome dysregulation, which can occur both in patients with FMF[8] and in patients with acute COVID infection.[9] Given the potential for effective therapy, clinicians should obtain a thorough fever history and consider genetic testing for autoinflammatory diseases in children experiencing post-COVID recurrent fevers.

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