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Case Report

A patient heterozygous for R92Q mutation with periodic fever and aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome-like phenotype

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SUMMARY: Batu ED, Sönmez HE, Bilginer Y, Özen S. A patient heterozygous for R92Q mutation with periodic fever and aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome-like phenotype. Turk J Pediatr 2018; 60: 726-728.

Tumor necrosis factor receptor associated periodic syndrome (TRAPS) is an autosomal dominant disease caused by mutations located on the type 1 tumor necrosis factor receptor (*TNFRSF1A*) gene. Here we present a 3-year-old boy heterozygous for R92Q mutation in *TNFRSF1A* gene expressing a periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome-like phenotype. However, some of his symptoms such as myalgia and the long duration of fever attacks were not typical for PFAPA. He was treated with methylprednisolone during the attacks and also responded to colchicine. The family history revealed that his grandfather, mother, and uncle suffered from similar attacks, and interestingly all of them responded to tonsillectomy. PFAPA-like features have already been reported in patients with the R92Q mutation. However, this case is interesting with the response to colchicine treatment and response to tonsillectomy in his relatives.

Key words: periodic fever with aphthous stomatitis, pharyngitis, and adenitis, tumor necrosis factor receptor associated periodic syndrome, R92Q mutation.

Tumor necrosis factor receptor associated periodic syndrome (TRAPS) is an autosomal dominant disease caused by mutations located on the type 1 tumor necrosis factor receptor (*TNFRSF1A*) gene.[1] Patients are characterized by long-lasting fever attacks, accompanied with rash, myalgia, abdominal pain, pericarditis, periorbital edema.[2] More than 90 mutations have been described in *TNFRSF1A,* however the phenotype of the disease may be different in each individual (http://fmf.igh.cnrs.fr/infevers/).[3,4] Most of the mutations are structural mutations which have high penetrance and encode the extracellular cysteine-rich domain (CRD). However the R92Q variant is a missense and low-penetrance mutation without effect on the structure or function of the protein and has high frequency among Caucasian children with periodic fever.[5,6] This variant is associated with a milder phenotype characterized with short attack duration, high tendency to spontaneous resolution, lower prevalence of amyloidosis and less frequent family history of periodic fever.[2,6]

Here, we present a patient heterozygous for R92Q mutation in *TNFRSF1A* gene with periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome-like phenotype.

Case Report

A 1-year-old boy presented with fever attacks, lasting 7-10 days with abdominal pain, arthralgia, aphthous stomatitis, pharyngitis, and myalgia. Initially, he was diagnosed with PFAPA, and received methylprednisolone (1 mg/kg/day) during the attacks and his attacks improved with this treatment. His acute phase reactants were high. Although he was negative for mutations of the *Mediterranean fever* gene, colchicine was started at another center (0.5 mg/day) and the attacks improved with this

therapy. Two years later, when he was 3 years old, he was admitted to our hospital. He had been suffering from a febrile attack lasting for 12 days and protracted myalgia. On physical examination, his temperature was 38.9°C, he had aphthous stomatitis and bilateral cervical lymphadenopathy. His complete blood count showed hemoglobin was 12.3 g/dl (11.5-14.5), white blood cell count 10800/mm^3 (4000-12000), and platelet count was 326000/mm^3 (150000-450000). C-reactive protein and erythrocyte sedimentation rates were 4.6 mg/dl (normal range, 0-0.8 mg/dl), and 46 mm/hour (0-20), respectively. Muscle enzymes were normal [creatine kinase, 88 (<145), lactate dehydrogenase, 232 (<247), aspartate aminotransferase, 12 (<52)].

Features such as myalgia and the long duration of fever attacks were considered atypical for PFAPA. A heterozygous p.Arg121Gln (c.312 G>A) (R92Q) mutation was detected in the *TNFRSF1A* gene. He responded to short term corticosteroid therapy (2 mg/kg/day;4 days). In the family history; he was the second child of consanguineous parents (first cousins) and his grandfather, mother, and uncle suffered from similar attacks, and interestingly the affected members had no attack after tonsillectomy. Parents, siblings (two sisters) and uncle of the patients were screened for mutations in *TNFRSF1A* gene. The patent's mother, uncle and one sister were heterozygous for p.Arg121Gln (c.312 G>A) (R92Q) mutation. However, the sister was healthy and had no symptoms related with periodic fever syndromes. This could be due to different penetrance of the mutation in different members of the family.

When the patient was admitted to the hospital, his parents gave informed consent approving genetic analyzes and anonymous data use for academic purpose.

Discussion

Patients heterozygous for R92Q mutation display various phenotypes ranging from TRAPS to PFAPA-like symptoms. Pelagatti et al.[6] compared the clinical and laboratory features of TRAPS patients (including 11 patients with structural mutations and 20 patients with R92Q) with PFAPA patients and found that phenotypes of TRAPS patients with R92Q mutation might resemble PFAPA; however, PFAPA patients had significantly shorter attack period, more frequent attacks per year, earlier age of disease onset, and higher rate of periodicity than PFAPA-like TRAPS patients. Patients with structural mutations had frequently more severe symptoms such as abdominal pain, skin rash, and myalgia. They also reported that a significant portion of patients with R92Q mutation experienced spontaneous resolution (25%) or amelioration of fever attacks (56%) like PPAFA patients.[6] Our patient had an early disease onset like PFAPA; however the duration of fever attacks was long and the fever was usually accompanied with myalgia. Family history of TRAPS is more frequent in patients who carried structural mutations than patients with R92Q mutation.[2,6] However, our patient had three affected family members. In previous studies, it was shown that patients with R92Q mutation had good response to short term steroid (on-demand therapy).[2,6] Interestingly, our patient improved with colchicine treatment. However, spontaneous remission was also reported in patients with R92Q heterozygous mutation. One more case with R92Q mutation had been reported from our center with similar features of PFAPA.[7]

The interesting features of our case were improvement with colchicine treatment and response to tonsillectomy in his relatives. Patients with R92Q mutation of *TNFRSF1A* may display milder phenotype and resemble PFAPA.

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