

## Different presentations in patients with tumor necrosis factor receptor-associated periodic syndrome mutations: report of two cases

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Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal dominant autoinflammatory disorder caused by mutations in the *TNFRSF1A* gene encoding the 55-kDa receptor for tumor necrosis factor (TNF)- $\alpha$ . It is characterized by recurrent prolonged episodes of fever accompanied by abdominal pain, pleuritis, migratory skin rashes, fasciitis, headache, conjunctivitis, and periorbital edema. We report two children, one with a severe mutation in the *TNFRSF1A* gene causing the typical phenotype. The second patient had a homozygous R92Q-type mutation and displayed a periodic fever with aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome-like phenotype.

In the eastern Mediterranean region, TRAPS is probably underdiagnosed because of the overwhelming frequency of familial Mediterranean fever (FMF). However, TRAPS should be sought for in patients with atypical symptoms for FMF.

**Key words:** tumor necrosis factor receptor-associated periodic syndrome (TRAPS), periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome, familial Mediterranean fever (FMF).

Tumor necrosis factor receptor (TNFR)-associated periodic syndrome (TRAPS) is a rare autosomal dominant disorder characterized by recurrent prolonged episodes of fevers accompanied by abdominal pain, pleuritis, migratory skin rashes, fasciitis, headache, conjunctivitis, and periorbital edema. The most serious complication of TRAPS is the development of systemic amyloid A (AA) amyloidosis, with a reported incidence ranging from 14% to 25%<sup>1,2</sup>. The disease is caused by mutations in exons 2–3 and 4–5 of the Tumor Necrosis Factor Receptor Superfamily Member 1A (*TNFRSF1A*) gene on chromosome 12p13.2<sup>3</sup>. Most of the *TNFRSF1A* mutations reported in TRAPS patients are missense substitutions mainly affecting the highly conserved cysteine residues in the extracellular cysteine-rich domains (CRDs) involved in disulfide bond formation and in the folding of the extracellular portion of TNFR p55<sup>2-4</sup>. The mutations are

thought to be associated with long-lasting activation of TNF signals<sup>5</sup>. On the other hand, a frequent diagnosis among young children with periodic fevers is a non-monogenic autoinflammatory syndrome called periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome. Recently, mild mutations of TRAPS have been reported to display PFAPA syndrome-like phenotype when young<sup>6</sup>. We report two patients with variable clinical expressions of TRAPS, one caused by a disease-causing mutation and the other with atypical features and a homozygous R92Q mutation in the *TNFRSF1A* gene, suggesting that the latter variant may be responsible for a mild, atypical phenotype.

### Case Reports

#### Case 1

A four-year-old Iraqi male patient presented to

Hacettepe University Children's Hospital due to attacks of high fever and abdominal pain lasting almost 21 days since the age of one year. These attacks recurred every month and even increased to twice monthly in the last year. He also had recurrent arthralgias and myalgias sometimes with migratory rashes over the body. The myalgia was occasionally severe enough to leave him bedridden. His physical examination on admission was unremarkable except for height and weight below the 3rd percentile. His family history was negative for periodic fever syndromes.

Detailed examination for fever of unknown origin, including serological tests, cultures, baseline imaging studies, and bone marrow aspiration, revealed no pathological finding. Acute-phase reactants were moderately elevated during attacks. *MEFV* gene mutation analysis revealed heterozygosity for the E148Q mutation. Due to presence of recurrent long-lasting fever episodes accompanied by myalgia and sometimes rash, TRAPS was considered in the differential diagnosis. A trial of colchicine was started while he was analyzed for TRAPS mutations. Colchicine therapy resulted in some decrease in fever but the attacks persisted. Mutational screening of the *TNFRSF1A* gene revealed a C33G mutation. The patient was first put on etanercept treatment. Since he did not respond, he was later switched to anakinra.

## Case 2

A 3.5-year-old Caucasian female patient suffering from periodic fever and abdominal pain lasting for a couple of days in the last two years was referred to Hacettepe University Children's Hospital. She also had recurrent arthralgias and myalgias during the attacks. Her physical examination on admission was unremarkable except for height and weight below the 3rd percentile. Her family history was unremarkable.

Acute-phase reactants were moderately elevated during attacks as was the serum AA level. Genetic analysis of the *MEFV* gene revealed no mutation. A therapeutic trial of colchicine 1 mg/day resulted in some benefit; however, she continued to suffer from an attack once monthly and she failed to gain any weight. Since she was unresponsive to colchicine, genetic analysis for TRAPS was carried out. A molecular diagnosis

of TRAPS confirmed a homozygous R92Q-type mutation. She responded to prednisone treatment during the attacks and was fine in the interim periods. She received a short course of etanercept since one of her attacks was prolonged and she had to receive rather large doses of steroid. Surprisingly, she failed to respond clinically to etanercept. However, her attacks subsided subsequently and she did not need a prolonged therapy.

## Discussion

Tumor necrosis factor receptor (TNFR)-associated periodic syndrome, the most common autosomal dominant autoinflammatory disorder, is caused by mutations in the *TNFRSF1A* gene encoding the 55-kDa receptor for TNF- $\alpha$ <sup>3</sup>. Thus far, more than 103 different variants of the *TNFRSF1A* gene have been reported and more than 80 different *TNFRSF1A* mutations have been found to be associated with TRAPS (Infervers database, online at: <http://fmf.igh.cnrs.fr/infervers>). Mutations in the *TNFRSF1A* gene cause defective shedding of surface TNFR, and increased signaling through the TNFR. Most mutations in the TNFR occur in the extracellular domain and affect receptor folding and trafficking, resulting in the retention of misfolded TNFR complexes in the endoplasmic reticulum<sup>2-5</sup>. Increased nuclear factor (NF)-[kappa]B activation and inflammation or a defect in TNF-induced leukocyte apoptosis is also suggested to play a role in the disease pathogenesis<sup>7,8</sup>.

The median age of onset is 10 years, ranging from 1 to 63 years. Presently, diagnosis is based on clinical manifestations and positive gene mutations. Attacks usually initiate with often severe myalgia that migrates in a centrifugal pattern, followed by fever with skin, joint, abdominal, and sometimes ocular manifestations. The duration of attacks in TRAPS is usually longer than seven days<sup>1,9</sup>. In TRAPS, arthralgia is more common than arthritis, in contrast to familial Mediterranean fever (FMF). The typical rash of TRAPS is a migratory erythematous patch and differs from the erysipelas-like erythema of FMF<sup>1</sup>.

Therapy for TRAPS includes glucocorticoids, TNF- $\alpha$  blockers, and interleukin (IL)-1 antagonist, with variable success<sup>1,10-14</sup>. Etanercept reduces symptoms and serum

levels of inflammatory markers of TRAPS in a dose-dependent manner<sup>12</sup>. The IL-1 receptor antagonist anakinra has been shown recently to prevent disease relapses in both the short- and long term and to induce a prompt and stable disease remission in etanercept-resistant patients<sup>14</sup>.

The first case we report had a disease-causing TRAPS mutation and was also heterozygote for E148Q in the *MEFV* gene. The second patient, with a homozygous R92Q mutation in the *TNFRSF1A* gene, presented with milder symptoms. The *MEFV* gene mutation analysis was negative.

Although E148Q mutation in the *MEFV* gene is also accepted as a polymorphism by many authors<sup>15</sup>, it has been associated occasionally with the FMF phenotype in certain individuals or it predisposes to inflammation<sup>16</sup>. Kogan et al<sup>17</sup>. Reported an excess of febrile episodes in Ashkenazi carriers of E148Q. On the other hand, R92Q is a low-penetrance mutation. The R92Q allele frequency has been reported in 1.8% to 3.3% in patients with clinical symptoms suggestive of TRAPS, especially in sporadic cases, and in 1% of healthy individuals<sup>2,4</sup>. Most patients carrying the R92Q mutation display a milder disease course and lower incidence of amyloidosis, but there are such TRAPS cases harboring a R92Q mutation with a more severe phenotype and incomplete responsiveness to non-steroidal antiinflammatory drugs, steroids, and TNF- $\alpha$  blockers<sup>10</sup>. On the other hand, there have been case reports with full-blown forms of TRAPS who have the R92Q substitution<sup>11</sup>. Thus, in the case of E148Q of FMF or the R92Q of TRAPS, certain genetic and environmental factors may be enhancing a state of inflammation, albeit a mild phenotype. The jury is out for a final decision.

Pelagatti et al.<sup>6</sup> reported young patients with PFAPA who had the R92Q mutation. In fact, our second patient with the R92Q mutation displayed a PFAPA-like phenotype and had a good response to steroids. On the other hand, in our population, in which FMF is very frequent, we find an increased heterozygosity for *MEFV* mutations among young children with PFAPA (personal observation). It is tempting to speculate that these mild mutations act as predisposing factors/modifying genetic factors for PFAPA.

In the eastern Mediterranean, FMF is frequent, and thus physicians often tend to diagnose periodic fever patients as FMF, even if they lack typical features. However, these cases remind us that TRAPS should be sought for in patients with atypical findings.

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