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CASE REPORT

A novel TNFRSF1A gene mutation in a patient with tumor necrosis factor receptor-associated periodic syndrome

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Abstract
Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is a periodic fever syndrome inherited in an autosomal dominant fashion. It stems from mutations in the *TNFRSF1A* (accession number: NM_001065) gene expressing the receptor for tumor necrosis factor α. A patient with TRAPS may present with prolonged episodes of fever attacks, abdominal pain, severe myalgia, and painful erythema on the trunk or extremities. Here, we report an 8-year-old boy with febrile attacks occurring every 1–2 months and continuing for 3–4 days. The patient experienced 40 °C-fever attacks without chills. Approximately 80% of fever attacks were accompanied by abdominal manifestations. Direct sequencing analysis was used to assess the genomic DNA of the patient, and a heterozygous R426L mutation in exon 10 of the *TNFRSF1A* gene in an autosomal dominant inheritance fashion was identified. Further genetic analyses were also carried out on his parents. Due to the fact that the mutation was not inherited from the parents, it was likely that R426L was a *de novo* and novel mutation in the *TNFRSF1A* gene, which can trigger TRAPS or TRAPS-like symptoms.

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Introduction

Tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS) is a periodic fever syndrome and patients may present with recurrent episodes of fever that normally last for 1—3 weeks, in addition to severe localized inflammation [1].

TRAPS arises from mutations of the tumor necrosis factor receptor 1 gene (*TNFRS1A*) (accession number: NM_001065) [2—5]. It was demonstrated that mutations of the *TNFRSF1A* gene at 12P13.2 exert a pivotal role in susceptibility to the disease [3,6,7]. TRAPS is inherited in an autosomal dominant fashion, and genetic heterogeneity and variable penetrance are well documented in this regard. Mutational analysis is required for confirmation of the diagnosis. Multiple mutations have by far been detected in the *TNFRSF1A* gene; of which 70 are associated with TRAPS [1,5,8].

Here, we report a case of TRAPS carrying an R426L mutation in exon 10 of the *TNFRSF1A* gene. Presumably, it is the first case of TRAPS reported in Iran and the first R426L mutation in exon 10 giving rise to TRAPS.

Case report

The present case report was approved by the Ethics Committee of Tabriz University of Medical Sciences, Iran. Informed consent was obtained from legal representative of the patient for disclosure of the patients' data. This case was an 8-year-old boy who presented with a 2-year periodic fever to the Outpatient Periodic Syndromes Clinic, Connective Tissue Diseases Research Center (CTRC), Imam Reza Hospital, Tabriz University of Medical Sciences (Tabriz, Iran). Roughly 80% of fever attacks were accompanied by abdominal manifestations. Febrile attacks occurred every 1—2 months and the patient complained of fever for 7—10 days. During the attack, the patient had a 40 °C fever without chills. Except mild abdominal tenderness, no other physical problems such as pharyngitis, skin lesions, and lymphadenopathy were observed during the attacks. Attacks were not responsive to colchicine, although they responded dramatically to steroids. No abnormality was diagnosed by clinical examination or by routine laboratory tests between the attacks; however, the patient showed leukocytosis and high erythrocyte sedimentation rate during the attacks. It is worth noting that this patient had a 1-year-old sister with the same recurrent fever attacking every 1 or 2 months. There was a negative familial history of periodic fever syndromes for the patient.

Tests and measurements

The patient and his parents were referred to the CTRC for further examination. DNA was extracted from the patient's leukocytes using a salting out technique, and mutation analysis was carried out by direct sequencing of two MEFV and *TNFRSF1A* genes. Evaluation of the genetic results showed no positive mutations for MEFV; however, a mutation was detected in exon 10 of *TNFRSF1A*, resulting in a substitution of leucine for arginine at residue 426 (R426L). The affected phenotype led to amino acid alterations and was heterozygous as a variant with unknown clinical significance. To confirm whether the mutation was responsible for the symptoms, the same molecular analysis of the *TNFRSF1A* gene was carried out on the parents. The final results showed that the mutation was only present in the patient but not in his parents (Fig. 1).

Discussion

TRAPS is the second most common periodic fever syndrome inherited in an autosomal dominant fashion. Mutations of the *TNFRSF1A* (12P13.2) gene have been demonstrated to bring about the disease [1]. To date, six missense mutations have been discovered in the target gene subsequent to the identification of the candidate locus [4]. Elsewhere, four novel mutations in *TNFRSF1A* have been detected [9]. This led to screening of 18 families with patients afflicted with TRAPS-like features [10]. The authors identified three previously reported and eight novel mutations in the gene and concluded that the genetic basis in affected members was heterogeneous.

More than 144 different *TNFRSF1A* gene mutations have thus far been identified as causes of TRAPS (fevers database: http://fmf.igh.cnrs.fr/infevers). Most of these mutations are found in exons and introns 2, 3, 4, and 6, as well as mutations in exons and introns 1, 5, 7, 8, and 10. Such mutations normally diminish shedding of *TNFR1* and eliminate an endogenous antagonist to circulating tumor necrosis factor (TNF), resulting in long-lasting activation of TNF signals, although in some patients, other mechanisms are present as follows: (1) an excess of retained surface *TNFR1* leading to a higher susceptibility to TNF [11]; (2) impaired TNF-driven apoptosis because of less efficient binding of mutant receptor to TNF [12] (3) giving rise to an unfolded protein response or initiating TNF-independent signaling in the cell by misfolded mutant *TNFR1* [13].

The disease usually occurs in childhood. Typically, the mean age of patients is 3 years [14]. The patients may suffer from recurrent episodes of fever normally lasting

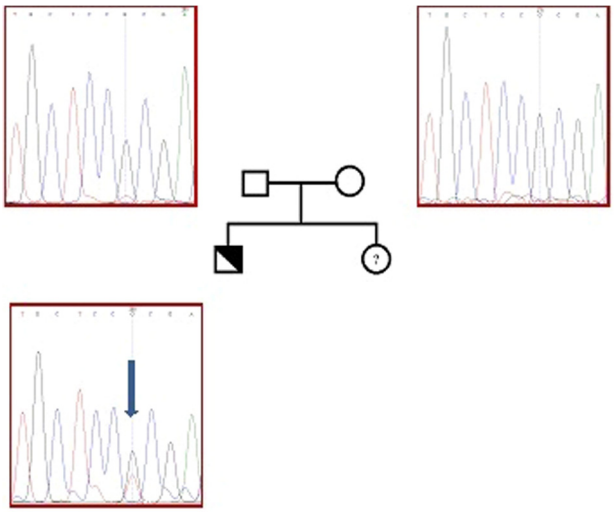

Fig. 1 New *TNFRSF1A* mutation (R426L) and pedigree of the tumor necrosis factor receptor-associated periodic syndrome family.

for 1—3 weeks, as well as severe localized inflammation [1]. Other symptoms including focal myalgia and sometimes migratory myalgia, conjunctivitis, periorbital edema, abdominal pain, monoarthritis, and rash are usually present with fever attacks [1]. Approximately 15% of patients may develop secondary AA (Amyloid A) amyloidosis, which primarily affects the kidneys [14].

TRAPS is diagnosed by a history of episodic fever and one or more accompanying symptoms. The long duration of fever attacks, rash, eye, periorbital involvement, and focal myalgia are hallmarks of TRAPS [14]. Family history is commonly positive in such patients, in spite of the fact that some carriers of TRAPS mutations do not show any symptoms. The clinical diagnosis of TRAPS is confirmed by genetic assessment of common mutations of the *TNFR1* gene.

The reported case was an 8-year-old boy experiencing recurrent fevers. Because of negative mutations in the MEFV gene, long duration of attacks, inefficacy of colchicine in the control of attacks, and good response to steroids, symptoms favored a possibility of TRAPS. Tests for *TNFRSF1A* gene mutations showed a novel mutation in exon 10, leading to the amino acid substitution and the affected phenotype (R426L). The parents also underwent the tests to ensure the pattern of inheritance and the results were negative for the parents. As the unaffected parents did not carry the R426L mutation while the patient did, the results indicated a strong possibility of this unique mutation responsible for the symptoms. Three mutations in exon 10 have by far been reported as a cause of TRAPS. These include L330L, Y331X, and R341R from France, Turkey and The Netherlands, respectively (in fevers database: http://fmf.igh.cnrs.fr/infevers). It appears that R426L is a novel mutation of the *TNFRSF1A* gene, which can cause TRAPS or TRAPS-like symptoms.

In conclusion, patients with TRAPS or TRAPS-like symptoms mostly carry mutations in the *TNFRSF1A* gene; however, in the reported case, R426L was likely to be the target mutation, as it was not inherited from the parents. Nevertheless, further case documentation and research is recommended.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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