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A novel mutation in TNFRSF1A associated with overlapping features of tumour necrosis factor receptor-associated periodic syndrome and hyper-IgD syndrome

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ABSTRACT

We describe a 10-year-old child with a novel mutation, c.352A>G/p.Thr118Ala (T89A) in the tumour necrosis factor receptor superfamily 1A (TNFRSF1A) gene. The patient presented with periodic fevers beginning at 2 years of age. He had overlapping clinical and laboratory features of tumour necrosis factor receptor-associated periodic syndrome (TRAPS) and hyper-IgD syndrome (HIDS). This patient expands the clinical and genetic spectrum of TRAPS.

Introduction

Tumour necrosis factor receptor-associated periodic syndrome (TRAPS) is a dominantly inherited autoinflammatory condition caused by mutations in the tumour necrosis factor receptor superfamily 1A gene (TNFRSF1A) that encodes the 55kDa receptor for TNF-α (1, 2). TRAPS is characterised by periodic episodes of high fever lasting several days to several weeks. The onset of symptoms is usually in childhood, with a median age of 3 years, but occasionally fever and other symptoms do not appear until adulthood. In addition to fever, other features include rash, myalgia, arthralgia, arthritis, abdominal pain, chest pain, conjunctivitis and periorbital edema (3). TRAPS is complicated by amyloidosis in approximately 15% of patients (2, 3).

The hyper-IgD syndrome (HIDS) is a recessively inherited autoinflammatory condition caused by mutations in the mevalonate kinase (MVK) gene (4, 5). It is characterised by periodic fevers lasting 4–6 days, usually beginning in the first year of life. Associated clinical features include cervical lymphadenopathy, painful oral ulcers, abdominal pain, diarrhea, arthralgia and rash (6). The vast majority of patients with HIDS have increased serum IgD concentrations greater than 14 mg/dl, or 100 IU/ml (4, 6).

We describe a 10-year-old boy who presented with overlapping features of TRAPS and HIDS and a markedly elevated serum IgD concentration. The patient had a novel mutation, c.352A>G/p.Thr118Ala (T89A) in exon 4 of the TNFRSF1A gene. HIDS was excluded in the child by mutation analysis of the MVK gene. This report expands the clinical and genetic spectrum of TRAPS.

Case report

A 10-year-old boy presented with a history of periodic fevers beginning at 2 years of age. Initially, the fevers were infrequent, occurring 3 or 4 times per year, and lasting 3–4 days. As a young child, he had few, if any other symptoms, associated with the fevers. Beginning at 7 years of age, the fevers became more frequent, prolonged and stereotypical. Since that time, he has had a fever up to 40°C every 2-3 weeks and lasting 5–7 days. Approximately 90% of the febrile episodes are associated with a sore throat and painful cervical lymphadenopathy. Painful oral ulcers accompany the febrile episodes approximately 50% of the time. Most fever episodes are associated with a macular rash on the neck or upper torso. The rash typically appears toward the end of the febrile episode and resolves within several days. The febrile episodes are almost always associated with myalgia and arthralgia of the knees or ankles. On several occasions, he had mild, transient swelling of a knee or ankle with the fever. The arthralgia typically occurs late in the course of the fever and resolves within 2 days after the resolution of the fever. The febrile episodes are not associated with abdominal pain, chest pain, scrotal pain, conjunctivitis or periorbital edema. The fever and other symptoms resolve within 48 hours after the administration of one or two doses of prednisone (1 mg/kg/dose) at the onset of fever. He is asymptomatic between episodes of fever.

Physical examination shortly after a febrile episode was normal except for mild cervical lymph node enlargement. Laboratory studies obtained shortly after an episode of fever showed a white blood cell count of 12,300/mm^3 with 85% neutrophils and 20% lymphocytes. The haemoglobin concentration was 13.5 gm/dl and the platelet count was 352,000/mm^3. The erythrocyte sedimentation rate was 39 mm/hr and the serum C-reactive protein concentration

was 14.9 mg/dl. Serum immunoglobulin concentrations revealed an IgG of 1430 mg/dl (633–1280), an IgA of 267 mg/dl (33–202), an IgM of 81 mg/dl (48–207) and an IgD of 45 mg/dl or 322 IU/ml (<14 mg/dl or <100 IU/ml). A repeat IgD level 4 months later was 65 mg/dl.

The patient's mother and father are Caucasian of Irish and Italian heritage respectively. Neither parent has a history of periodic fevers or other symptoms suggestive of TRAPS.

HIDS was excluded in the patient by mutation analysis of all exons and flanking intron sequences of the MVK gene. The patient was then screened for mutations in the extracellular domain of the TNFRSF1A gene that have been associated with TRAPS. The patient had a novel mutation, c.352A>G/p.Thr118Ala (T89A) in exon 4 of the TNFRSF1A gene. This new TRAPS-associated mutation was not present in any of the 345 ethnically matched control DNA samples or in the patient's mother. The father was not available for genotyping.

Discussion

The patient in this report had a number of clinical features that were characteristic of TRAPS, but he also exhibited some features that were suggestive of HIDS. Painful cervical lymphadenopathy and oral ulcers are present more frequently in HIDS than in TRAPS. In addition, our patient had a markedly elevated serum IgD concentration on two occasions. Serum IgD levels are elevated in the vast majority of patients with HIDS. However, not all patients with HIDS have elevated IgD concentrations (4, 7). Moreover, increased IgD levels have been reported in other patients with TRAPS (8, 9).

HIDS was excluded in our patient by mutation analysis of the MVK gene. To date, there are no reports of HIDS patients with diminished MVK enzyme activity in whom the MVK gene mutation analysis was normal. Simon *et al*. (10) reported 13 patients with clinical features of HIDS with normal MVK enzyme activity. None of the patients had mutations in the MVK gene. The patient in this report illustrates that there may be considerable overlap in the clinical and laboratory features of TRAPS and HIDS. TRAPS should be considered in patients with clinical and laboratory features of HIDS in whom MVK genotyping is normal.

The patient in this report had no other affected family members. Although TRAPS is typically a dominantly inherited condition, Dode *et al*. (9) found that only 32% of patients with TRAPS had a family history of recurrent inflammatory syndromes. Moreover, Aganna *et al*. (11) reported a *de novo* mutation in the TNFRSF1A gene in a patient with TRAPS. We do not know whether our patient had a *de novo* mutation since his father was not genotyped.

More than 50 mutations in the TNFRSF1A gene have been reported in patients with TRAPS (12). The vast majority of mutations reported in TRAPS are missense nucleotide changes in exons 2–4, and they affect the first two cysteine-rich domains of the extracellular portion of the TNF-α receptor (TNFR1) (2, 12). Some mutations, particularly those involving cysteine residues, lead to defective TNFR1 shedding from the cell surface (1-3). This results in diminished soluble receptors available to bind TNF and abrogate the inflammatory response. However, other mutations do not affect receptor shedding (2, 3). Thus, defective receptor shedding does not explain the pathophysiology of autoinflammation in all patients with TRAPS. Our understanding of the pathogenesis of TRAPS has recently been advanced by *in vitro* experiments utilising over expression of TNFR1 mutant receptors in various cell lines. These studies showed that TRAPS-associated mutant receptors were retained intracellularly and were incapable of trafficking to the cell surface (13, 14). *Ex vivo* studies of TNFR1 expression in cells from TRAPS patients have produced differing results. One study showed intracellular retention of mutant receptors (15). However, Nedjai *et al*. (16) showed a high concentration of the TNFR1 receptors at the cell surface and enhanced sensitization to TNF signalling.

The functional consequences of the mutation in our patient are unknown. The T89A mutation replaces a polar amino acid, threonine for a hydrophobic amino acid, alanine. Based on the sequence homology of TNFRSF1 and TNFRSF2, threonine 89 is a residue conserved between TNF receptors 1 and 2 and it is proximal to the highly conserved cysteine residue at position 88 that has been associated with two different TRAPS causing mutations (C88R and C88Y). Thus, along with cysteine 88, threonine 89 may be important for the three-dimensional structure and folding of the extracellular domain of TNFRSF1A. The absence of the T89A mutation in controls strongly suggests that it is a disease-causing mutation.

In summary, this report expands the genetic spectrum of TRAPS, and it adds to the clinical features associated with TRAPS.

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