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ORIGINAL PAPER

TNF receptor-associated periodic syndrome (TRAPS): Description of a novel *TNFRSF1A* mutation and response to etanercept

Adriana A. Jesus · João B. Oliveira · Ivona Aksentijevich · Erika Fujihira · Magda M. S. Carneiro-Sampaio · Alberto J. S. Duarte · Clovis A. A. Silva

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Abstract TRAPS is the most common of the autosomal dominant periodic fever syndromes. It is caused by mutations in the *TNFRSF1A* gene, which encodes for the type 1 TNF-receptor (TNFR1). We describe here a Brazilian patient with TRAPS associated to a novel *TNFRSF1A de novo* mutation and the response to anti-TNF therapy. The patient is a 9-year-old girl with recurrent fevers since the age of 3 years, usually lasting 3 to 7 days, and recurring every other week. These episodes are associated with mild abdominal pain, nausea, vomiting and generalized myalgia. Recurrent conjunctivitis and erysipela-like skin lesions in the lower limbs also occur. Laboratory studies show persistent normocytic normochromic anemia, thrombocytosis, elevated erythrocyte sedimentation rate and C-reactive protein. IgD levels are normal. Mutational screening of *TNFRSF1A* revealed the association of a novel C30F mutation with the common R92Q low-penetrance mutation. The R92Q mutation is seen in 5% of the general population and is associated with an atypical inflammatory phenotype. The patient had a very good response to etanercept, with cessation of fever and normalization of inflammatory markers. Our report expands the spectrum of *TNFRSF1*A mutations associated with TRAPS, adding further evidence for possible additive effects of a low-penetration R92Q and cysteine residue mutations, and confirms etanercept as an efficacious treatment alternative.

Keywords Periodic fever · TNF-receptor · Hibernian fever · Mutation · TNFRSF1A

Abbreviations

TRAPS	TNF-receptor-associated periodic syndrome
TNFRSF1A	tumor necrosis factor receptor superfamily 1A gene
MEFV	Mediterranean fever gene
MVK	mevalonate kinase gene
FMF	familial Mediterranean fever
HIDS	hyper IgD with periodic fever syndrome
CAPS	cryopyrin-associated periodic fever syndromes
FCAS	familial cold autoinflammatory syndrome
MWS	Muckle-Wells syndrome

Adriana A. Jesus and João B. Oliveira contributed equally to this work.

A. A. Jesus · C. A. A. Silva (✉)
Pediatric Rheumatology Unit, Pediatrics Department,
University of São Paulo,
Av. Dr. Enéas de Carvalho Aguiar, 647,
05403-900 São Paulo, SP, Brazil
e-mail: clovisaas@icr.hcnet.usp.br

M. M. S. Carneiro-Sampaio
Pediatrics Department, University of São Paulo,
Av. Dr. Enéas de Carvalho Aguiar, 647,
05403-900 São Paulo, SP, Brazil

J. B. Oliveira (✉) · E. Fujihira · A. J. S. Duarte
Molecular Immunology and Genetics Section,
Laboratory of Medical Investigation 56 (LIM-56),
University of São Paulo,
Av. Dr. Enéas de Carvalho Aguiar, 500, IMT BII 3rd floor,
05403-000 São Paulo, SP, Brazil
e-mail: oliveirajb@lim56.fm.usp.br

I. Aksentijevich
Genetics and Genomic Branch, National Institutes of Arthritis and Musculoskeletal and Skin Diseases,
10 Center Drive, Bldg. 10, Room 9N214,
Bethesda, MD 20892, USA

CINCA/ NOMID	chronic infantile neurological cutaneous and articular syndrome
CRD	cysteine rich-domain
FUO	fever of unknown origin

Introduction

The autoinflammatory syndromes are characterized by recurrent episodes of fever, as well as inflammation of several organs and tissues, such as skin, serosal linings, joints, gut and eyes [2, 12]. These syndromes are distinguished from autoimmune diseases by the absence of high-titer autoantibodies or self-reactive T cells. At present, the main autoinflammatory syndromes include: familial Mediterranean fever (FMF; OMIM 249100), tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS; OMIM 142680), cryopyrin-associated periodic syndromes (CAPS) and hyper IgD syndrome with periodic fever (HIDS; OMIM 260020) [2, 15]. Another frequent, but non-hereditary autoinflammatory syndrome is periodic fever, aphtous stomatitis, pharyngitis and adenitis (PFAPA). These conditions are among the rheumatologic causes of fever of unknown origin (FUO) in children, being of importance to the practicing pediatrician. TRAPS and the other hereditary autoinflammatory syndromes are summarized in Table 1.

We describe here a patient with the second most common periodic fever syndrome, TRAPS, caused by a novel mutation (p.C30F) in *TNFRSF1*A and successfully treated with an anti-TNF agent.

Case report

The patient is a 9-year-old girl referred in February 2006 to the pediatric rheumatology unit. She has had a clinical history of recurrent fever since the age of 3 years, characterized by low-grade temperature (38°C/100.4°F) for 3 to 7 days and recurring every other week. Fever episodes were associated with mild abdominal pain, nausea, vomiting and generalized myalgia. The patient also presented recurrent conjunctivitis and erysipela-like skin lesions in the lower limbs. Extensive prior evaluation included negative investigations for infectious etiologies such as toxoplasmosis, cytomegalovirus, herpes virus, rubella and HIV. Past laboratory studies showed persistent normocytic normochromic anemia, thrombocytosis, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). She tested positive for antinuclear antibodies (ANA), 1:80, and negative for rheumatoid factor. Echocardiogram, abdominal CT and colonoscopy were normal. There was a maternal family ancestor of German origin, four generations in the past. The remaining family members were born and raised in Brazil. Family history is negative for periodic fever syndromes, but positive for thyroiditis (father), idiopathic hematuria (mother) and asthma (brother).

Physical examination at admission was unremarkable, except for height in percentile 3 and weight in percentile 10–25. Laboratory exams showed mild microcytic anemia, leukocytosis with neutrophilia and thrombocytosis (Table 2). In addition, inflammation markers were elevated (Table 1), ANA was positive (1:160) and anti-DNA was negative. Serum amyloid A level measurement is not available at our center. Liver function tests, electrolytes, BUN, creatinine and urinalysis were normal. Urinary protein loss was 0.29 g/24 h. Eye examination and bone and joint X-rays were normal. IgD level was within normal range (1.07 mg/dl). Mutation analysis for familial Mediterranean fever excluded the five most common MEFV mutations: M680I, M694V, M694I, V726A and E148Q.

Mutational screening of the *TNFRSF1A* gene revealed the novel c.176G>T mutation in exon 2, leading to a cysteine to phenylalanine change at position 30 of the protein (Fig. 1). This mutation disrupts the second disulfide chain in the first cystein-rich domain (CRD1) of the extracellular portion of the receptor (Fig. 2). Interestingly, the patient is also a carrier of the common p.R92Q (c.362 G>A) low-penetrance mutation, which has been previously associated to an atypical inflammatory phenotype. Her father and mother do not carry the pathogenic C30F mutation, indicating a *de novo* event. However, the father is a carrier for the R92Q low penetrance mutation, but has never presented recurrent inflammatory symptoms.

Prior to admission at our service, the patient received several courses of non-steroidal anti-inflammatory drugs, such as naproxen and indomethacin, with partial clinical response. As etanercept was not available at that time and the patient persisted with frequent fever episodes impairing her quality of life, a trial with colchicine was started in July, 2006, although this is not the therapy of choice for this disease. One month after starting therapy, a slight decrease in the frequency of fever episodes was observed, as well as a decrease in platelet numbers, although ESR and CRP values remained high. Given the partial response to colchicine, the treatment was discontinued, and the patient was started on anti-TNF therapy with etanercept (human recombinant p75 receptor-IgG fusion protein) in March, 2007. The response to etanercept was excellent, and 2 months later cessation of fever was observed, with a return of the inflammatory markers, platelet counts and hemoglobin to normal levels (Table 2). The patient also achieved a significant improvement of her quality of life.

Table 1 Genetics, clinical findings and treatment of the main hereditary periodic fever syndromes

	FMF	HIDS	TRAPS	NOMID	MWS	FCAS
Inheritance	Recessive	Recessive	Dominant	Dominant	Dominant	Dominant
Gene affected	*MEFV*	*MVK*	*TNFRSF1A*	*CIAS1*	*CIAS1*	*CIAS1*
Usual ethnicity	Jewish, Armenian, Arab, Turkish, Italian	Dutch and other Northern European	Northern European or any ethnicity	Any ethnicity	Northern European	European
Duration of attaks	1–3 days	3–7 days	>1 week	Continuous, with flares	24–48 h	<24 h
Cutaneous	Erysipeloid erythema on lower leg, ankle, foot	Diffuse maculopapular rash, purpura, petechiae	Migratory rash, underlying myalgia	Urticaria-like rash	Urticaria-like rash	Cold-induced urticarial rash
Ocular	Rare	Uncommon	Conjunctivitis ou periorbital edema	Uveitis, conjunctivitis, papilledema, progressive vision loss	Conjunctivitis, episcleritis, optic disk edema	Conjunctivitis
Muscle-skeletal	Monoarthritis, sacroileitis	Arthralgia, symmetric polyarthritis	Migratory myalgia, arthralgia, non-erosive monoarthritis	Epiphyseal overgrowth, chronic arthritis	Myalgia, arthralgia, oligoarthritis	Myalgia, arthralgia
Gastrintestinal	Sterile peritonitis - 85%	Abdominal pain, vomiting, diarrhea	Abdominal pain, peritonitis, diarrhea, constipation	Hepatosplenomegaly	Abdominal pain	Nausea
Typical findings	Pleuritis, pericarditis, scrotal pain	Cervical adenopathy, IgD elevation, urinary mevalonate	Pleuritis	Mental retardation, chronic non-septic meningitis, headache, sensorineural deafness	*S*ensorineural deafness	Headache
Amyloidosis	Common	Rare	10%	Some patients in adulthood	10-50%	Uncommon
Treatment	Colchicine, steroids for refractory myalgia	NSAIDS, steroids, etanercept, statins	NSAIDS, steroids, etanercept	Anakinra	Anakinra, NSAIDS, steroids	Cold avoidance, anakinra

FMF, familiar Mediterranean fever; HIDS, hyper-IgD syndrome; TRAPS, TNF receptor-associated periodic syndrome; NOMID, neonatal-onset multisystemic inflammatory disease; MWS, Muckle-Wells syndrome; FCAS, familial cold-associated autoinflammatory syndrome

Discussion

TRAPS is the most common of the autosomal dominant periodic fever syndromes, and second only to familial Mediterranean fever as the most prevalent autoinflammatory syndrome overall [17]. It is caused by mutations in the *TNFRSF1A* gene, located on chromosome 12p13, which encodes the type-1 TNF receptor [13]. This receptor is the main mediator of signaling by TNF-α, thus being a crucial component of the inflammatory cascade. Binding of TNF-α to TNFR1 activates several pathways, with diverse outcomes, including NF-κB activation and inflammation or apoptosis, both supposedly involved in the hyperinflammatory state found in TRAPS patients [12, 15].

Table 2 Laboratory findings at admission and 3 months after etanercept was started

	Admission	Post-etanercept
Hemoglobin, g/l	10	12.8
Leukocyte count, 10^9/l	13.1	9.9
Neutrophil count, 10^9/l	8.5	4.0
Platelet count, 10^9/l	721	296
CRP, mg/dl	91.2	0.6
ESR, mm1h	56	5

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate

Characteristic clinical features of TRAPS include recurrent prolonged fevers, abdominal pain, migratory myalgia, cutaneous inflammation and ocular symptoms. The median age of onset is 10 years, ranging from 1 to 63 years. The fever episodes last usually >1 week and are frequently associated with abdominal pain (77%), localized myalgia (63%), erythematous/erysipela-like rash (55%) and ocular symptoms, such as periorbital edema, conjunctivitis or

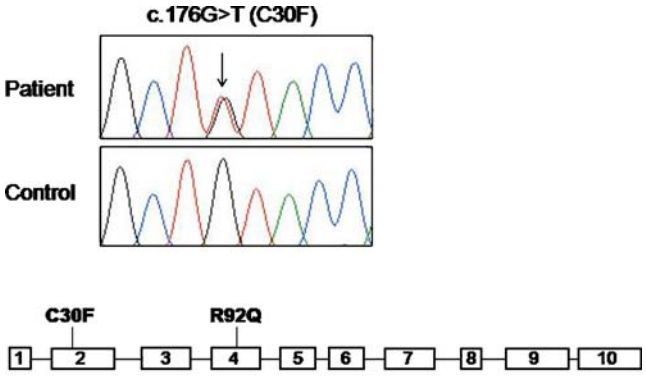

Fig. 1 *TNFRSF1A* C30F and R92Q mutations in a patient with TRAPS. Upper panel, G to T base substitution in exon 2, causing a cysteine to phenylalanine change at the protein position 30; lower panel, schematic diagram showing the localization of the C30F and R92Q mutations in the *TNFRSF1A* cDNA

uveitis (48%). Further symptoms include arthralgia/arthritis in 51% and pleuritis in 32% of patients. The most common laboratory findings are the elevation of acute phase reactants, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen and serum A amyloid (SAA), not only during fever attacks, but often also during symptom-free intervals. This sustained inflammation increases the risk of secondary amyloidosis, a complication seen in up to 14% of the patients [1, 7, 12, 16]. The main clinical findings, genetics and treatment options for the hereditary periodic fever syndromes are presented on Table 1.

Disease associated-mutations in *TNFRSF1A* are exclusively clustered in the extracellular domain of the receptor, encoded by exons 2, 3, 4 and 6 [1, 7]. There are currently more than 51 different disease-associated mutations reported (INFEVERS database: http://fmf.igh.cnrs.fr/ISSAID/infevers/ *Accessed 2007-09-27*), mostly single-nucleotide or missense substitutions. We describe here a patient with two simultaneous mutations in TNFR1 resulting in TRAPS symptoms. The C30F mutation has not been previously described in TRAPS patients, although there are three other mutations described in the literature affecting the same residue (C30R, C30Y, C30S) [4, 11, 18]. Dodé et al. described three family members with the C30S substitution and a spectrum of clinical symptoms. One member of the family was asymptomatic, while the other two presented with recurrent fever and localized myalgia. One of the symptomatic individuals had a spontaneous remission of the disease, whereas the other presented a more severe clinical course with intense inflammatory response and failure of both etanercept and infliximab therapy [4]. Takagi et al. also reported three family members (mother and two siblings) with the C30R substitution. Whereas the woman presented with a periodic high-grade fever, skin rash and lymphadenopathy only after the third decade of life, her elder son had presented inflammatory symptoms (fever, skin rash and arthralgia) since he was 7 months old. The younger sibling had presented periodic fever since 3 years of age [18]. Although a positive family history has been found in 82% of the known TRAPS mutations, our patient presented a de novo mutation. De novo events were also observed in patients carrying T50K, G36E, Y20D and C70R mutations [17].

Cysteine mutations are generally associated with a higher penetrance and a more severe phenotype, including a higher risk for the development of amyloidosis [1, 15]. Our patient has presented with recurrent fever associated to myalgia, ocular and skin manifestations with impairment of her quality of life. She also has presented mild proteinuria, which might be related to renal amyloidosis [1].

Our patient is also a carrier for the R92Q mutation, which has the carrier frequency of 2–4% in various Caucasian populations [1, 7]. Compared to mutations affecting disulfide bonds of the extracellular domains, R92Q appears to have a significantly lower penetrance, and it is associated with a milder and more variable phenotype. Although in general the risk for amyloidosis and chronic renal failure is much lower, there are reports of early chronic renal failure and kidney transplant in patients harboring this mutation [3, 6, 15]. Jacobelli et al. described a 27-year-old woman with recurrent severe abdominal and thoracic pain, high-grade fever, arthritis and cutaneous rash since the age of 5 years, harboring only R92Q mutation. Moreover, this patient did not present any improvement with infliximab therapy [9]. In our patient, besides the novel and probably more disease-relevant C30F mutation, the R92Q substitution might have contributed to her clinical phenotype, as Haas et al. also observed in a woman with both R92Q and F60V substitutions [6].

The patient received several courses of different NSAIDs and colchicine without success, as experienced by others [7, 10]. She was then initiated on etanercept, with excellent

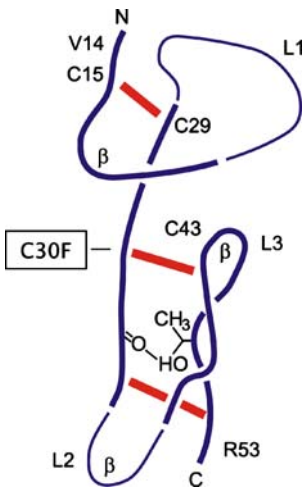

Fig. 2 Crystallographic structure of the type-1 TNF receptor extracellular domain 1 [2]. The three disulfide bonds of CRD1 are depicted by thick red bars. The C30F substitution disrupts the second disulfide bond inside the first extracellular CRD domain, predictably causing conformational changes in the extracellular domain

response. Etanercept, the soluble p75 TNFR:Fc fusion protein, is effective in reducing, although usually not totally eliminating, clinical and laboratory evidence of inflammation in TRAPS [10]. Previous studies reported the role of anti-TNF therapy in preventing amyloidosis and possibly inducing its regression [5]. However, control of acute-phase response was not sufficiently achieved in all cases [8, 17]. Additionally, there are many reports of secondary failure of etanercept, indicating a need for long-term monitoring. Blocking IL-1β with anakinra works better than blocking TNF for some TRAPS patients, suggesting a role for both TNF-dependent and -independent pathways in the pathogenesis of TRAPS [14]. Therefore, etanercept and anakinra combination therapy may be necessary to inhibit the exacerbated inflammatory response and secondary amyloidosis, which is the most threatening complication found in these patients.

Our report expands the spectrum of *TNFRSF1*A mutations associated with TRAPS and adds further evidence for possible additive effects of a low-penetration R92Q and cysteine residue mutations.

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